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RAPID IDENTIFICATION OF MALIGNANT CELLS IN VAGINAL SMEARS BY CYTOPLASMIC FLUORESCENCE

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THE FLUORESCENT DYE acridine orange (AO) was introduced by Strugger in 1940. Subsequently, it was shown that this dye had an affinity for both of the nucleic acids, but particularly ribonucleic acid (RNA). Actively proliferating cells, such as those present in embryonic or malignant tissue, have an increased amount of RNA compared with their normal adult counterparts. There is evidence also that increased cytoplasmic RNA accompanies nuclear changes in proliferating malignant cervical squamous epithelial cells. The amount of RNA of normal squamous epithelium decreases as the cells cornify.

In 1956, Bertalanffy and associates (1) described a technique in which acridine orange was used to estimate qualitatively cellular RNA and, in addition, to provide morphologic detail. The method was rapid and simple and resulted in polychromatic fluorescence of cervical squamous epithelium. The nuclear chromatin, which fluoresced green to yellow, provided a contrasting background for an orange nucleolus. The cytoplasm fluoresced green, orange, or intense red-orange, depending on the amount of RNA present. In gynecologic smears, the cytoplasm of certain exfoliated malignant cells fluoresced a characteristic intense red-orange. On the other hand, the cytoplasm of other malignant cells, which presumably had lost some of their RNA, fluoresced a nonspecific orange or red. The procedure was said to be applicable to mass programs for detection of uterine cancer because it required neither a highly trained screener nor a long screening time.

In 1958, Bertalanffy and associates (2) reported correct identification of malignant cells in AO stained smears from 56 to 58 patients with uterine cancer. However, there has been no report which gives the percentage of smears containing malignant cells which can be identified by characteristic red-orange fluorescence alone without using conventional morphologic criteria of malignancy. The present study was de-

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signed to evaluate acridine orange fluorescence of cytoplasm as a screening test for uterine malignant neoplasms, with the view that it might be used to eliminate most normal smears, selecting only suspicious smears for cytologic examination by routine Papanicolaou methods. In this report are discussed the results of examination of 864 AO stained smears from 641 unselected patients without disease or with diagnoses which included untreated and postirradiated uterine carcinoma, cervicitis, and pregnancy.

MATERIALS AND METHODS

Between July and December 1958, 864 smears were obtained from 641 unselected gynecologic and obstetric patients at the University of Minnesota Hospitals. There were 326 patients from the Cancer Detection Center, 172 from gynecology tumor clinic, 128 from the gynecology and obstetric clinics, and 15 gynecology inpatients. Those from the Cancer Detection Center represented a group of asymptomatic women. Patients from the gynecology tumor clinic had been treated previously for malignant neoplasms and were examined during this period for possible recurrence of tumor. Patients from the gynecology clinic had been referred by other hospital services for evaluation of routine pelvic complaints. The 15 inpatients had various gynecologic disorders.

The collection routine was adapted to existing procedures in each clinic. Smears were taken by the physician or medical student who made the initial examination. A duplicate smear was made for independent examination by the Cancer Detection Center or Gynecology Department using conventional Papanicolaou methods. Vaginal aspirations were taken from all patients, and, in addition, cervical scrapings were obtained from many of the Cancer Detection Center patients. Slides from the Cancer Detection Center and inpatient service were coded so that neither the patient's name nor hospital number were known to the AO screener. Those from the other clinics contained the patient's name and hospital number. The clinical history and diagnosis, biopsy report, and Papanicolaou diagnosis were not known prior to examination of the AO stained smears.

The slides were fixed immediately in 95 per cent ethanol. Most slides were stained after 3 to 4 hours in the fixative, although some remained in 95 per cent ethanol for as long as 1 month. Ten slides were stained simultaneously by the following method, modified after Bertalanffy (1):

1. 80 per cent ethanol: 10 dips or 10 seconds
2. 70 per cent ethanol: 10 dips or 10 seconds
3. 50 per cent ethanol: 10 dips or 10 seconds
4. Distilled water: 10 dips or 10 seconds
5. 1 per cent acetic acid: 10 dips or 10 seconds (retards subsequent fading)
6. Distilled water: 10 dips or 10 seconds
7. 0.01 per cent acridine orange (National aniline) in *p*H 6 phosphate buffer: 3 minutes

8–10. *p*H 6 phosphate buffer: 10 dips each or 30 seconds, (decolorization)

11. 0.1 M $CaCl_2$: 45 seconds (differentiation)
12. Mount in *p*H 6 phosphate buffer and coverslip
13. Read wet within 1 hour; slides not permanent

Reproducible colors in exfoliated vaginal cells were obtained consistently by this procedure, as detailed by Bertalanffy (2). The 3 minute staining time was found to be critical. It was found that 3 dishes of *p*H 6 phosphate buffer were necessary to remove excess dye from a slide. The *p*H must be 6 when this dye concentration and short staining time are used in order to produce a spectrum of suitable color in the cytoplasm. The *p*H 6 buffer is made by adding 5.60 cubic centimeters of 0.1 normal sodium hydroxide to 50 cubic centimeters of 0.1 molar monopotassium phosphate and bringing the total volume to 100 cubic centimeters with distilled water. It is possible to make several gallons of buffer at a time which may be stored at room temperature provided the solution is dispensed by siphonage or filtered before use. The buffer dishes in steps 8 through 10 must be changed frequently as they become less efficient in removing dye after 30 to 40 slides have been

passed through. Other dishes of solution must be changed frequently in order to remove contaminating dye which causes undesirable background fluorescence.

At the end of step 10, all of the material on a slide stains orange. After 45 seconds in 0.1 molar calcium chloride, nonspecific staining of protein is removed, and a green to yellow nucleus with an orange nucleolus is left. The cytoplasm of exfoliated squamous epithelium fluoresces green, orange, brick-red, or intense red-orange (Figs. 1 and 2) while that of endocervical epithelium fluoresces bright orange (Fig. 3). The vaginal flora (orange-staining bacteria, monilia, trichomonas) and the yellow-green nuclei of leucocytes may be observed also (Fig. 2). Erythrocytes are not stained by this method. If desired, slides can be destained in 50 per cent ethanol and restained by conventional Papanicolaou methods.

A Spencer monocular microscope, equipped with a plain aluminized mirror, quartz condenser, and yellow ocular suppression filter, was used for examination of the smears. The light source was a Zeiss-Winkel lamp containing an HBO 200 (Osram) mercury arc bulb. One 5113 and 2 BG 12 primary filters, which transmit near ultraviolet and blue-violet light, were used. Incident intensity was standardized by adjusting the condenser diaphragm until the background was black under high dry magnification. Slides were scanned initially under low power. Only suspicious areas were scrutinized under high dry power Staining and screening were performed by an observer with a background in pathology but no training in cytology. Ten slides were stained and read in 1 hour, photography time not included. Photographs were taken on 120 super anscochrome film with an exposure time of 5 minutes; original magnification of all photomicrographs, ×315.

Legends for color insert

(Magnifications all reduced to ×280.)

FIG. 1. Normal vaginal superficial squamous cells. Most of the cells in smears from normal patients contained green to orange cytoplasm strikingly different from the intense red-orange of malignant cells. Yellow nuclei are shown. AO negative. Vaginal aspiration.

FIG. 2. Normal basal cell with orange cytoplasm is present in the lower portion of the field. A cigar-shaped, orange-staining trichomonas is demonstrated, together with yellow-green nuclei of polymorphonuclear leucocytes. AO negative. Vaginal aspiration.

FIG. 3. Normal endocervical epithelium. Note bright yellow-orange cytoplasm and ghostlike outlines of mucous globules. The green background is an artifact caused by contaminating AO present in the buffer mounting medium. Such buffer should be changed frequently. AO negative. Vaginal aspiration.

FIG. 4. Case 1. Squamous cell carcinoma of the vagina. Two malignant cells with intense red-orange cytoplasm are shown in the center of the field. Compare color and intensity of this cytoplasm with that of the normal basal cell shown in Figure 2. Many such cells were seen under low magnification. Yellow nuclei of polymorphonuclear leucocytes are scattered throughout the field. AO positive. Vaginal aspiration.

FIG. 5. Case 2. Adenocarcinoma of the endometrium. Note 2 malignant secretory cells in the center of the field with intense red-orange cytoplasm which includes faint, green-stained goblets of mucus. Faint orange cytoplasm of a degenerated cell is seen immediately above. Green nuclei of polymorphonuclear leucocytes are shown. AO positive. Vaginal aspiration.

FIG. 6. Case 5. Adenocarcinoma of the endometrium. Intense red-orange cytoplasm is shown as a brilliant orange in this reproduction of 3 cells. Pale orange cytoplasm is seen in degenerated cells together with small orange amorphous clumps representing cytoplasm of lysed cells. Green nuclei of polymorphonuclear leucocytes are present in the field. AO positive. Vaginal smear material.

FIG. 7. Case 6. Undifferentiated carcinoma of the cervix. Note malignant cells with large yellow nuclei. Intense red-orange cytoplasm is seen. A dense cluster of yellow-green polymorphonuclear leucocytes is present; these must be carefully screened. Scattered orange cocci are present. AO positive. Vaginal smear.

FIG. 8. Case 7. Three cells from a squamous cell carcinoma of the cervix. Intense red-orange granular cytoplasm and yellow pleomorphic nuclei are shown. Compare size of these cells with green nuclei of polymorphonuclear leucocytes. AO positive. Vaginal aspiration.

FIG. 9. Cells from a postirradiated squamous cell carcinoma of the cervix. Detail obscured in printing of photomicrograph but few yellow nuclei of these cells could be seen on a background of cytoplasm which was intense red-orange. Yellow-green nuclei of polymorphonuclear leucocytes encircle the cervical cells. False AO positive. Vaginal aspiration.

FIG. 10. Cluster of cocci which may be confused with malignant cells. Note absence of a nucleus. Compare size of the cluster with the green nuclei of polymorphonuclear leucocytes. AO negative. Vaginal aspiration.

FIG. 11. Normal gastric cells from body of stomach. Note pale orange cytoplasm and yellow-green nuclei. Touch preparation.

FIG. 12. Gastric adenocarcinoma. Note intense red-orange cytoplasm and yellow nuclei. Orange nucleoli not well demonstrated. Touch preparation.

A positive diagnosis of malignancy was made when the cytoplasm of several cells fluoresced an intense red-orange. All other slides were called negative. There was no intermediate category. Slides which contained only a few cells, or, as in 1 case, only material from a rectovaginal fistula, were called inadequate.

In summarizing the results, an AO diagnosis was called correctly positive when there was corresponding clinical, biopsy, and Papanicolaou diagnosis of malignancy. A slide called negative was considered correct when all other evidence cited was negative. The AO diagnosis was considered to be false positive if intense red-orange cellular cytoplasm was observed but there was no clinical, biopsy, or Papanicolaou evidence of malignancy. When no intense red-orange cytoplasm was seen but all other evidence was positive, a false negative AO diagnosis was made.

RESULTS

The results are summarized in Table I. During the 5 month period included in this study, there were 12 patients in which clinical, biopsy, and Papanicolaou evidence indicated malignancy. Only 7 of the 12 (58 per cent) had positive AO diagnoses on initial vaginal aspiration. A correct positive diagnosis of adenocarcinoma of the endometrium was made in 3 patients (Cases 2, 4, and 5), of squamous cell carcinoma of the vagina in 1 patient (Case 1), of squamous cell carcinoma of the cervix in 2 patients (Cases 3 and 7), and of undifferentiated carcinoma of the cervix in 1 patient (Case 6). No cervical scrapings were obtained from these patients. Two of the 12 patients had recurrent, postirradiated, squamous cell carcinoma of the cervix, neither of which was identified by AO fluorescence. Of the 5 primary squamous cell carcinomas of the cervix, 3 were called correctly AO positive. Three of the 4 adenocarcinomas of the endometrium and the undifferentiated carcinoma of the cervix were positive. Thus, 7 of 10 (70 per cent) primary malignant neoplasms were identified properly by AO fluorescence of cytoplasm. These cases are briefly summarized below:

CASE REPORTS

CASE 1. A 65 year old para 3-0-1-3, whose last menstrual period occurred at age 42, had a history of vaginal spotting of several months' duration. Examination disclosed a bleeding lesion on the right vaginal wall. The clinical diagnosis of carcinoma was confirmed by biopsy which showed squamous cell carcinoma of the vagina. Papanicolaou smear was positive. AO smear indicated many positive cells (Fig. 4).

CASE 2. A 64 year old para 2-0-0-2, whose last menstrual period occurred at age 49, was seen in July 1958 with a history of postmenopausal bleeding. A Papanicolaou smear was interpreted as negative for tumor cells. Diagnostic dilatation and curettage in August 1958 indicated an endometrial polyp. The patient returned to the gynecology clinic in September 1958 with the complaint of persistent lower abdominal pain. Pelvic examination revealed an endometrial polyp which was removed. The uterine corpus at this time was enlarged to the size of a 16 to 18 week pregnancy. A second dilatation and curettage was performed 9 October. Gross and microscopic diagnosis at this time was endometrial adenocarcinoma. A review of the initial Papanicolaou smear and curettings showed that malignancy had been present in July 1958. An AO smear taken 10 October 1958 revealed many positive cells (Fig. 5).

CASE 3. A 36 year old para 2-0-0-2, whose last menstrual period occurred 5 November 1958, was well until that time, when she had a prolonged and profuse menstrual period lasting 9 days. Her private physician performed a dilatation and curettage. Microscopic sections showed squamous cell carcinoma of the cervix. Physical examination on admission to University Hospitals revealed a friable, partially necrotic, exophytic cervical tumor. Clinical and pathologic diagnosis (biopsy) was squamous cell carcinoma of the cervix, League of Nations stage II. Papanicolaou smear was positive. AO smear indicated a few positive cells.

CASE 4. A 61 year old para 2-0-0-2, whose last menstrual period occurred at age 45, had had moderate postmenopausal vaginal bleeding for a few days in August 1957. Bleeding recurred in March 1958, and by December 1958 there was a bloody vaginal discharge which "soaked" several pads daily. Pelvic examination showed an enlarged soft cervix. The os was dilated. The uterine fundus was 1½ to 2 times enlarged, soft, mobile, and regular in contour. Material from a dilatation and curettage revealed an adenocarcinoma of the endometrium. Papanicolaou smear was positive. AO smear showed few positive cells.

TABLE I.—RESULTS OF ACRIDINE ORANGE SCREENING IN 641 PATIENTS

		Positive		Negative		False positive		False negative		Inadequate smears		Per cent accuracy*
	Total	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	
Normal	326	0	0	324	99.5	2	0.5	0	0	0	0	0
Gyn. tumor clinic	172	0	0	156	90.7	5	2.9	2	1.2	9	5.2	0 (0/2)
Gyn. and obst. clinic	128	1	0.8	117	91.4	3	2.3	1	0.8	6	4.7	50 (1/2)
Gynecology inpatients	15	6	40	6	40	1	6.7	2	13.3	0	0	75 (6/8)
(641 smears)	641	7		603		11		5		15		58.4 (7/12)

*Per cent accuracy = $\frac{\text{No. correct AO positive}}{\text{No. known positive}} \times 100$

CASE 5. A 47 year old para 0-0-0-0, whose last menstrual period occurred in 1957, had had prolonged and irregular vaginal bleeding in the winter of 1957. In May 1957, a "panhysterectomy" was performed elsewhere for "carcinoma of the ovary." She was well until July 1958 when there was onset of vaginal bleeding which increased in quantity. Pelvic examination revealed that the apex of the vaginal vault was replaced by a friable, granular, necrotic tumor with central ulceration. Biopsy disclosed adenocarcinoma of the endometrium with extension to the vaginal vault. Papanicolaou smear was positive. AO smear showed a few positive cells but much lysis (Fig. 6).

CASE 6. A 72 year old para 8-0-0-6, whose last menstrual period occurred at age 49, was well until September 1958, when a routine pelvic examination by her private physician revealed a suspicious area on the cervix. A biopsy was performed and was positive for carcinoma. Pelvic examination at the University Hospitals revealed a healing biopsy site and reddened cervical os. Biopsy demonstrated undifferentiated carcinoma of the cervix. Papanicolaou smear was positive. AO smear showed several positive cells among many polymorphonuclear leucocytes (Fig. 7).

CASE 7. A 43 year old para 2-0-0-2, whose last menstrual period occurred on 6 October 1958, had had abnormal vaginal bleeding starting in February 1957 following an automobile accident. Profuse menses occurred every 2 to 3 months. Pelvic examination showed the cervix to be replaced by a necrotic, ulcerating, exophytic tumor. The clinical and pathologic diagnosis was squamous cell carcinoma of the cervix, League of Nations stage I. Papanicolaou smear was positive. AO smear showed few positive cells (Fig. 8).

There were 629 patients in whom no malignant neoplasm was present. In 15 of these, the smears were considered inadequate. Of the remaining 614 patients, 603 (98 per cent) were eliminated correctly. Of the 11 AO false positives, 6 were from cases of postirradiated squamous cell carcinoma of the cervix, 1 was from a pregnant patient, 1 from a patient with a healed cervical laceration, and 3 were from asymptomatic patients (Cancer Detection Center). Altogether, smears from 18 patients were called AO positive; 7 patients (44 per cent) actually had a malignant neoplasm.

DISCUSSION

The value of early diagnosis of uterine cancer by Papanicolaou smears is accepted, but conventional staining techniques are demanding in terms of time and the requirement of skilled cytoscreeners. In the past, Bertalanffy and his associates (1) have introduced fluorescent techniques, largely unsuccessful, to correct these problems. The technical advantages of AO fluorescence are fourfold. The rapid 6 minute staining time results in a polychromatic picture with a single dye, and the screening time is short. Furthermore, some malignant cells can be identified easily by characteristic flaming red-orange cytoplasm. With the addition of a reasonably inexpensive ultraviolet light source and a yellow filter in the ocular, a standard laboratory microscope can be used.

AO fluorescence might be an expedient for screeners already experienced in cytology, but certain refinements are necessary before a minimally trained observer can use this technique to identify uterine cancers accurately. In this series, only 7 of 12 malignant tumors were identified by characteristic fluorescence alone, even though all of the 12 were diagnosed correctly by means of rou-

tine Papanicolaou smears. However, as shown in Figures 4 through 8, the striking color can be recognized by an observer with minimal training in cytology. In 2 cases (Figs. 4 and 5), in fact, many such typical cells were seen even under low power. Furthermore, the incidence of AO false positives in a normal population is low (Table I). Certainly such a property would facilitate the operation of mass screening programs, although cells which give this reaction may not be present in all smears from patients with malignant tumors. Several factors which limit the number of AO positive cells which may be found in smears from patients with uterine cancer deserve consideration.

One of the major limitations of AO fluorescence is implied in the studies by Gross and Danziger, by Foraker, and by Moberger. Gross and Danziger, using Brachet's methyl green-pyronin technique, found increased cytoplasmic RNA only in the immature, rapidly dividing cells in cervical squamous carcinoma. Foraker demonstrated by photometry of hematoxylin and eosin preparations that cellular basophilia (RNA+DNA) was increased in both invasive and intraepithelial squamous cell carcinomas of the cervix. Moberger, using absorption spectrophotometry, demonstrated an increased concentration of cytoplasmic nucleic acid of infiltrating cells in rapidly growing epidermoid carcinomas as compared to homologous tissues of origin and slowly growing carcinomas. He pointed out also that some portions of a neoplasm have reduced amounts of RNA. Thus, it may be presumed that a vaginal aspiration from a patient with uterine cancer will contain only a certain proportion of AO positive malignant cells.

In this series only 2 of the correct AO positive (Cases 1 and 2) cases presented with large numbers of AO positive cells in the vaginal aspiration. One of these was from a patient with clinically early carcinoma (Case 1). The other was from a patient who had had a diagnostic dilatation and curettage the day preceding vaginal aspiration (Case 2). The presence of many cells in this specimen might have resulted from their disruption by this procedure. There were only a few characteristic cells in each of the other correct AO positive cases, but these had been exfoliated from grossly necrotic tumors (Cases 3, 4, 5, 6, and 7). The proliferating cells which are AO positive were undoubtedly diluted by the greater number of necrotic cells present in such tumors, and such cells do not stain an intense red-orange. Restricting the use of the AO fluorescent technique to the diagnosis of early squamous cells carcinomas of the cervix, which contain large numbers of proliferating cells, may increase markedly the proportion of positive cells obtained.

Other limitations of the technique are suggested by the reasons for 5 false negatives in this series. In 2 cases of squamous cell carcinoma of the cervix, the slides were in 95 per cent ethanol longer than 2 weeks. It was apparent at the time of staining that many cells had floated off the slide during rehydration but since many cells remained, a diagnosis was made. If these slides originally contained characteristic cells, it is possible that these were lost during the staining procedure. Staining slides within 2 to 3 days after fixation may thus prevent loss of positive cells.

In 1 smear from a case of squamous cell carcinoma of the cervix it was apparent that most of the cells were lysed, as manifested by many clumps of orange-staining material accompanying bare nuclei. Such a slide, which represents a grossly necrotic carcinoma, seldom presents characteristic fluorescence (Fig. 6). Such slides in the future should be rejected for AO diagnosis and conventional Papanicolaou stains should be used. Another squamous cell carcinoma of the cervix was missed because the entire slide was covered with orange-staining cocci (Fig. 10) which obscured the exfoliated cells. Similarly, a second smear should be obtained and stained by conventional techniques. An adenocarcinoma of the endome-

trium, which had been called negative on 3 previous Papanicolaou diagnoses, was missed. Although 3 out of 4 such tumors were positive in this series, they are known for their poor exfoliative properties, and the AO fluorescent method may not be adequate to identify them.

Occasionally, AO positive malignant cells are present but are difficult to see. Figure 7 illustrates malignant cells almost obscured by a thick layer of surrounding leucocytes. Thick areas on a slide must be screened carefully under high dry power. Circular clumps of bacteria, distinguished by their uniform granular appearance and absence of a nucleus, may superficially resemble positive malignant cells (Fig. 10). Finally, if incident intensity is not standardized carefully so that the background is black, orange-staining cells may be easily confused with malignant cells because of added cytoplasmic intensity.

Tissue cultures can be grown on coverslips and stained in the same manner as vaginal smears. Present evidence obtained from cell cultures indicates that AO fluorescence of cytoplasm reflects cellular proliferation. When human amnion cells are first cultured they are round, discrete, and sedentary, and their cytoplasm stains orange with AO. However, when these cells begin to proliferate, are pleomorphic, and are transplanted, their cytoplasm fluoresces an intense red-orange which is identical with the fluorescence of HeLa cells, a strain cultured from human cervical squamous cell carcinoma. Some investigators believe that such cells have undergone malignant-like transformation.

Since intense red-orange AO fluorescence of cytoplasm seems to characterize proliferating cells, it may be inferred that certain benign conditions which occur in the uterus might not be distinguished from uterine carcinoma. Bertalanffy and associates (2) stated that in AO stained smears certain benign uterine hyperplasias differed from malignant cells only by their normal morphologic properties. The present series includes 49 patients with benign uterine hyperplasias including chronic cervicitis, cervical erosion, endocervical polyp, chronic polypoid endocervicitis, vaginal papilloma, trichomoniasis, moniliasis, pregnancy, and abortion. Of this group, 1 patient with a threatened abortion and 1 patient with a healed cervical laceration were called AO positive. Even though certain AO stained cells from benign hyperplasias might present intense red-orange cytoplasm, this does not appear to be a practical limitation of the AO fluorescent technique. In this series, 98 per cent (603 of 614) of patients who had no uterine cancer were correctly identified (Table I). If necessary, conventional Papanicolaou procedures can be applied to destained AO slides for comparative diagnosis by a skilled cytologist.

Poorest results were obtained in smears from post-irradiated patients (Table I). Both cases of recurrent post-irradiated squamous cell cervical carcinomas were missed. More than 50 per cent (6 of 11) of the false positives in this series were from the post-irradiated group (Fig. 9). It has been shown by Mitchell (5, 6) that postirradiated cells may contain increased RNA, and this property may have contributed to this result. However, these patients should be followed up by standard procedures to determine if there is an earlier incidence of recurrence than that of a comparable postirradiated group.

These data suggest that an observer untrained in cytology will have the greatest probability of making a correct diagnosis from smears from malignant tumors which contain large numbers of actively proliferating cells. The unsuspected or early squamous cell carcinoma of the cervix is such a tumor and is the logical object of a mass screening program.

It is probable that other malignant neoplasms may be identified also by this technique. Figures 11 and 12 show touch preparations from normal gastric mucosa and from a gastric adenocarcinoma which are strikingly different in color. Future studies

are necessary to confirm the reliability of AO fluorescence in detecting malignant tumors in other organs.

CONCLUSIONS

Vaginal aspirations and cervical scrapings from 641 unselected gynecologic and obstetric patients were screened for uterine malignant neoplasms, with acridine orange fluorescence by an observer untrained in cytology. Presence of intense red-orange cytoplasmic fluorescence, which reflects an increased amount of ribonucleic acid, was considered presumptive evidence of malignancy. In 7 (44 per cent) of 18 such smears called AO positive, malignancy was actually present. Most AO false positives (6 of 11) were from patients with postirradiated squamous cell carcinoma of the cervix. Present evidence indicates that the increased RNA in a cervical squamous cell carcinoma occurs in rapidly proliferating cells. Reasons for false negatives are discussed. By restricting AO fluorescent screening to detection of early carcinomas which contain rapidly growing cells, it is conceivable that greater accuracy will be obtained.

The technique is rapid and simple. It appears to be valuable in screening a normal population in that there is a low percentage of false positive results. It does not appear to be of value in screening postirradiated patients for recurrence of malignant neoplasms. In this study, 70 per cent (7 of 10) of primary uterine malignant tumors were identified properly by AO fluorescence of cytoplasm.

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THE EFFECT OF ALTERATION OF LIVER BLOOD FLOW UPON EXPERIMENTAL HEPATIC METASTASES

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WHILE circulating tumor cells are being detected with greater frequency in individuals with neoplasms, opinion and evidence would suggest that such cells do not always form metastases. Precise factors responsible for the success or failure of growth of transplanted tumor cells are not known. Two principal theories, however, have achieved popularity—one supporting mechanical factors as determinants of the site and growth of metastases, and the other favoring the "soil" theory which relates metastatic development to environmental conditions. Many who have favored the latter concept of metastasis formation, as first proposed by Langenbeck and later by Paget in 1889, concerned themselves with the relation of blood supply to the relative frequency of metastatic growth in the various organs. Willis has suggested that the susceptibility of the liver to metastasis, when compared to other organs, might well be related to its poor oxygenation. Cameron, however, was less impressed with the importance of oxygen supply in the early stages of tumor spread, believing that only later, when ischema intervenes and cell growth is impeded and destroyed, is it vital.

To obtain information relative to the importance of blood and oxygen supply to the liver on the development of metastases we have altered the hepatic blood flow in animals by vena cava constriction, hepatic artery ligation, and portacaval shunt and have noted their effect on take and growth of artificially induced metastases in this organ.

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METHODS AND MATERIALS

All animals used in these experiments were Sprague Dawley female rats weighing between 150 and 200 grams, except for those in the portacaval shunt experiments which were larger—250 to 300 grams. They were housed in individual cages and permitted water and a standard laboratory chow diet ad libitum.

The tumor utilized was the Walker-256 carcinosarcoma. Preparation of tumor cell suspensions and the technique of intraportal injection were identical with those used by us in previous studies, already reported in detail (5). Animals subjected to one of the procedures used either for alteration of hepatic blood flow or tumor cell inoculation or both were lightly anesthetized with ether, subjected to celiotomy, and injected intraportally with ½ milliliter of a saline plasma solution containing 5,000 tumor cells by way of a large mesenteric vein. Experiments were devised so that control and experimental animals were injected with the same tumor cell suspensions.

Constriction of the inferior vena cava between the liver and diaphragm was accomplished by retracting the liver caudad, passing a No. 3–0 silk ligature around the cava with a curved hemostat, and tying around this vessel and an interposed hemostat. Upon withdrawal of the hemostat from the silk loop the cava was constricted, but not occluded, in a consistent fashion. All controls were subjected to sham operations whereby the cava was actually constricted for several minutes and then released.

In animals subjected to hepatic artery ligation, this vessel was dissected free from the bile duct and was ligated close to the hilum

TABLE I.—EFFECT OF VENA CAVA CONSTRICTION ON HEPATIC METASTASES

Groups	Time of partial constriction	No. of rats	Metastases: No. +	Metastases: No. −	Metastases: Per cent +	Grade of tumor growth: +1	+2	+3
A	Just prior to tumor cell injection	21	21	0	100	4	6	11
	Controls	24	9	15	37	9	0	0
B	10 minutes after tumor cell injection	46	38	8	82	18	6	14
	Controls	33	17	16	51	13	4	0
C	2 days after tumor cell injection	41	31	10	75	20	8	3
	Controls	30	12	18	40	11	1	0

TABLE II.—ALTERATION OF HEPATIC BLOOD FLOW AND BROMSULPHALEIN (BSP) CLEARANCE

	Time after alteration of hepatic blood flow: 24 hrs.	72 hrs.	7 days	14 days
Normal nonsurgical controls	9.4 ± 0.05*	—	—	—
Hepatic artery ligation	13.9 ± 1.0 P<0.01	15.8 ± 1.0 P<0.01	16.4 ± 1.5 P<0.01	—
Sham operation	10.9 ± 0.6 P<0.01	9.6 ± 1.0 P = 0.6	—	—
Vena cava constriction	15.7 ± 1.1 P<0.01	12.0 ± 0.7 P = 0.05	17.6 ± 1.5 P<0.01	—
Sham operation	10.5 ± 0.8 P<0.01	10.1 ± 0.5 P = 0.1	—	—
Portacaval shunt	56.2 ± 3.9 P<0.01	59.2 ± 2.6 P<0.01	69.7 ± 2.3 P<0.01	70.7 ± 10.4 P<0.01
Sham operation	12.8 ± 0.4 P<0.01	12.0 ± 1.0 P<0.01	9.6 ± 0.3 P = 0.2	9.6 ± 0.3 P = 0.2

*All values are per cent BSP retention 5 minutes after I.V. injection of 1 mgm./100 gm. body weight.
Value after ± denotes S.D.
All P values compared with normal controls.

of the liver so as to eliminate anastomotic vessels as a source of hepatic arterial blood supply. The phrenic-hepatic ligament through which small arterial channels traverse was severed for the same reason. Control animals were subjected to identical sham operations, except that the hepatic artery was not ligated.

All of the portacaval shunts were performed by one of us (S.H.L.) who has perfected this procedure in the rat so that it may be accomplished with practically no mortality. End-to-side portacaval anastomoses were made, No. 7–0 continuous silk sutures being used in a fashion similar to that employed in humans. Venous occlusion clamps were in place for 10 to 12 minutes. Controls were subjected to mobilization of vessels and a similar period of venous occlusion.

Serum glutamic pyruvic transaminase (SGP-T) was measured colorimetrically by using the Reitman and Frankel modification of the method described by Wroblewski and Cabaud, and values are expressed as sigma-Frankel units. Bromsulphalein (BSP) clearance by the rat liver was evaluated by injecting BSP—1.0 milligram per 100 gram of rat—into the femoral vein and 5 minutes later removing a 1 milliliter blood sample from the opposite femoral vein. This amount of BSP and time for the sample collection were found most satisfactory after a variety of others had been used. The measurement of plasma concentration of BSP was performed by using a micromodification of the method of Gaebler.

At the time of sacrifice, 14 days after tumor cell injection, livers were examined for gross evidence of tumor, and metastases were arbitrarily graded as either +1, +2, or +3, depending upon their number and size.

RESULTS

Vena cava constriction (Table I). To evaluate the effect of hepatic congestion upon the take and growth of artificially induced hepatic metastases, the inferior vena cava was constricted between the liver and the diaphragm just before tumor cell inoculation (group A), 10 minutes after (group B), and 2 days after (group C).

Group A.—When the cava was partially occluded and the tumor cells injected a few minutes later, 100 per cent of the rats demonstrated metastases at sacrifice, whereas only 37 per cent of the control animals had tumor in the liver. Moreover, 17 of the 21 rats subjected to caval constriction had metastases graded as +2 or +3, while none of the 24 control animals was in this category (Fig. 1).

Group B.—When tumor cells were injected 10 minutes after partial caval occlusion the number of animals with tumor and

the size of growth at sacrifice were increased over that found for the controls (82 per cent in the former and 51 per cent in the latter). As in group A, larger tumors were found in those animals which were subjected to constriction.

Group C.—When constriction was effected 2 days after cell inoculation the results were the same as in the preceding two groups. Tumor was found in 75 per cent of the partially ligated animals when sacrificed on the fourteenth day after tumor inoculation. Thirty-three per cent were graded +2 and +3. Only 40 per cent of the controls were positive and only 8 per cent of these were graded larger than +1.

Hepatic artery ligation. The effects of ligation of the hepatic artery were evaluated in the following three experiments:

Group A.—Three days prior to tumor cell injection hepatic arteries in the experimental group of 48 rats were ligated, and the 48 control animals were subjected to sham operation. Fourteen days after tumor cell inoculation the animals were sacrificed, and 67 per cent of the artery-ligation animals demonstrated tumors in the liver. Only 38 per cent of the controls were positive. There was no apparent difference in the size of tumors; all, in both the control and the ligated groups, were +1.

Group B.—When the hepatic artery was ligated 10 minutes after intraportal injection of tumor cells, 65 per cent of the 40 experimental animals had liver metastases at the end of 14 days as compared to 22 per cent in the control group of 40 rats. No difference in tumor size was evident between the different groups.

Group C.—Three days after tumor cell injection 77 rats were subjected to hepatic artery ligation and 78 animals similarly were subjected to sham operation. After 2 weeks no difference in the incidence or in the size of metastases was observed between the two groups.

Portacaval shunt. Tumor cells were injected and portacaval shunts performed in 26 rats. Twenty-three subjected to sham operations served as controls. After 14 days no alteration in the incidence of metastases or size of tumor from that observed in control animals was evident. It was not technically feasible to inject tumor cells via the portal vein into the rats which had been subjected to prior shunting.

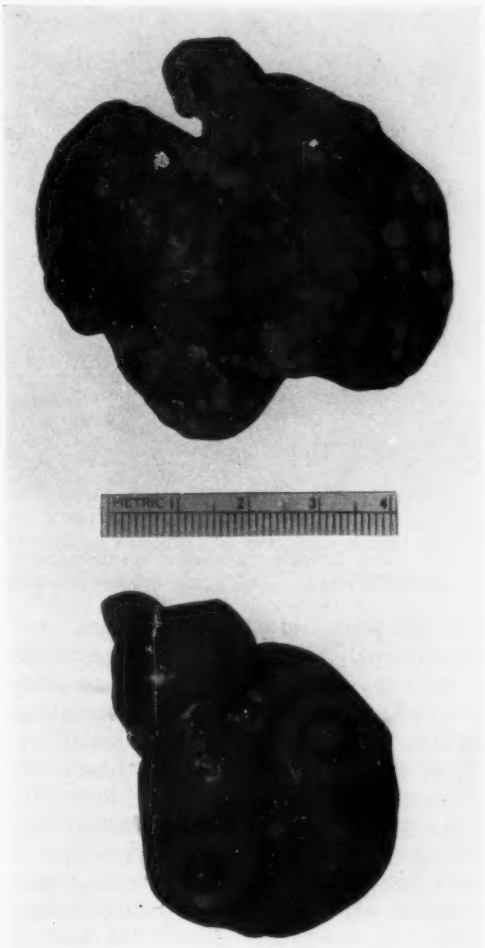

FIG. 1. Effect of vena cava constriction, prior to intraportal tumor cell injection, upon hepatic metastases. Liver from unconstricted animal below.

Liver function studies following alteration of hepatic blood supply (Table II). Interference with normal hepatic blood flow produced significant increases in SGP-T (Fig. 6).

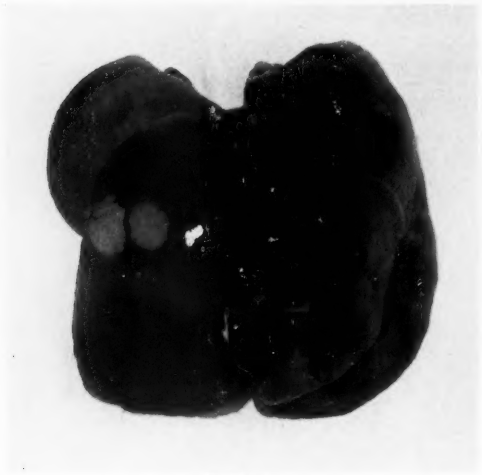

FIG. 2.

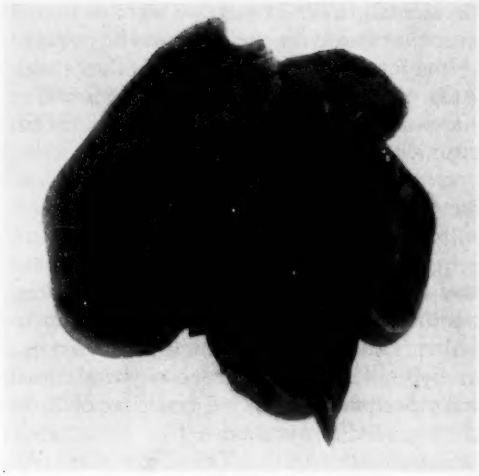

FIG. 3.

FIG. 2. India ink injection via the portal vein demonstrating lack of portal blood supply to metastases.

FIG. 3. India ink injection via the hepatic artery demonstrating the arterial blood supply of metastases.

Changes were also observed in sham operation animals. Such elevations were detected as early as 24 hours after vena cava constriction and persisted for as long as 7 days. After hepatic artery ligation no significant increase was observed in either the ligation or sham operation animals after 24 hours. By 72 hours, however, values were increased in both groups and remained so for at least 7 days. Portacaval shunt and sham shunt animals also exhibited changes. Fourteen days after shunting, the SGP-T was still elevated above normal ($P = .02$), but sham operation animals had normal values.

BSP clearance was slightly, but significantly, decreased over normal for as long as a week after vena cava constriction and hepatic artery ligation. Sham operation animals showed only a transient retention of BSP. Portacaval shunt rats exhibited a marked retention of BSP for as long as 14 days. While normal animals retained only 9.4 per cent 5 minutes after BSP injection, 56.2 per cent was still present 24 hours after shunting, and 70.7 per cent retention was observed 14 days after shunting. A slight increase in retention occurred in the animals studied 24 and 72 hours after sham operation (12.8 and 12.0 per cent, respectively).

Blood supply of liver metastases—injection studies. To ascertain whether the blood supply of hepatic metastases was predominantly arterial or venous in nature, the following experiments were carried out in animals whose livers displayed such tumor.

In 10 rats the hepatic artery was ligated close to the hilum of the liver, the portal vein cannulated, and India ink slowly injected under a minimum of pressure. All animals demonstrated a blackening of the hepatic parenchyma around the tumor and throughout the liver, but the metastatic nodule remained unchanged in color (Fig. 2). If, however, the portal vein (10 rats) was ligated at the hilum of the liver and the ink was injected into the aorta at the level of the celiac axis, tumors were seen to become black before discoloration of the surrounding liver was noted (Fig. 3). Microscopic confirmation was striking, as is evidenced by Figures 4 and 5. Identical findings were obtained when fluorescein solution was injected instead of the India ink and livers were observed with ultraviolet light.

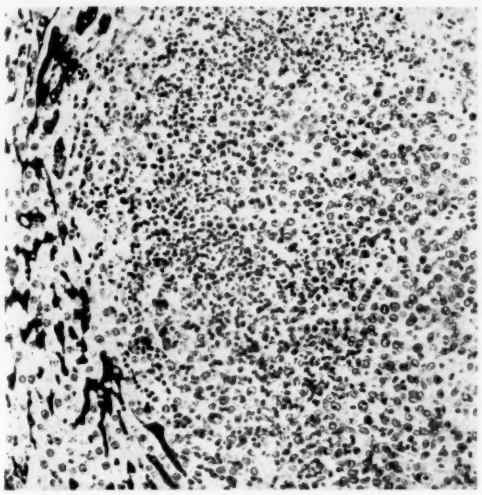

FIG. 4.

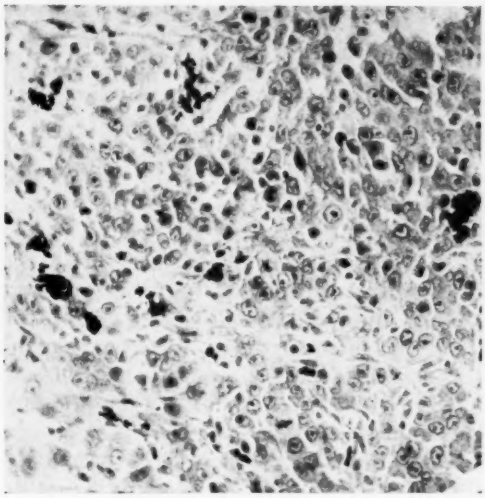

FIG. 5.

FIG. 4. Injection of India ink via the portal vein. Microscopic section of liver and tumor. Hematoxylin and eosin stain, ×55.

FIG. 5. Injection of India ink via the hepatic artery. Microscopic section of liver and tumor. Hematoxylin and eosin stain, ×105.

DISCUSSION

Few reports have been published relating tumor growth to available oxygen. Warburg (19) concluded that normal cells became cancerous because of a shift from aerobic to anaerobic respiration and reported (18) that the higher the rate of anaerobic glycolysis the more malignant the tumor. He also noted that although tumors have a high fermentation rate, they may be damaged by anoxia. Total agreement with Warburg is lacking, as evidenced in the article by Weinhouse. In 1942, Pollack and his associates reported that implantation of large bubbles of pure oxygen in the vicinity of tumors had no effect on their growth, and Barach and Bickerman in 1954 found that sarcomas transplanted to mice maintained in a low oxygen environment did not grow as well as in control animals.

Our observations that the shunting of portal blood away from the liver without interference with arterial supply had no effect, whereas an enhanced incidence and growth of tumor took place in livers that were deprived of arterial blood or were congested, would suggest that a decreased oxygen supply to that organ, as proposed by Willis, promotes the development of metastases. Such a result may be considered as being due to either a change in the tumor cell or an alteration of the hepatic "soil" produced by the reduced hepatic oxygenation, or both. No explanation is apparent from the data in these experiments to affirm or deny that the tumor cell is affected by the alteration in oxygen environment so that it "takes" and grows more readily. This theory remains a possibility and requires further investigation. On the other hand, implication of alteration of hepatic "soil" by reduction in oxygen supply as the reason for enhanced tumor growth is more readily substantiated. In a previous report by us (4) the relationship of various types of hepatic trauma to tumor growth was demonstrated. It is evident from the increased SGP-T and the BSP retention that the procedures resorted to in these experiments resulted in liver injury and a decrease in hepatic blood flow. While sham operation control animals also exhibited such changes, from these biochemical determinations it is

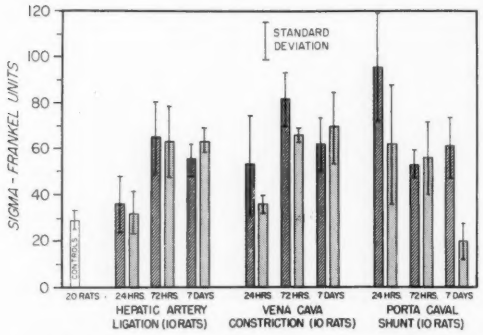

FIG. 6. Effect of alteration of hepatic blood flow upon serum glutamic pyruvic transaminase (SGP-T). Diagonal lined bars indicate operations; stippling, sham operations.

not possible to equate the degree of hepatic damage between the control and the experimental groups. However, histologic study disclosed evidence of greater hepatic injury, as characterized by foci of necrosis and an increase of mitotic activity in the experimental animals, particularly those animals with caval constriction and hepatic artery ligation.

The absence of enhanced metastases after portacaval shunt in spite of elevated SGP-T levels is worthy of comment. One possibility is that the hepatic injury was less severe than that which occurred in animals after caval occlusion or hepatic artery ligation. Another may well be related to the impairment of liver repair and regeneration which occurs after portacaval shunt. The possibility exists that enhancement of metastases after a variety of types of liver injury is not due to the injury per se but to the concomitant regenerative process that is known to take place. Much indirect evidence is available in the literature to suggest that a humoral factor is concerned with the process of liver regeneration. Paschkis and associates have reported that this humoral growth-promoting agent not only is limited to liver but may also enhance the growth of certain malignant tumors. Thus, the lack of such a factor may be similarly responsible for the failure of liver regeneration and the augmentation of hepatic metastases in the portacaval shunt animal. If this be so, it would be possible to unify the seemingly divergent opinions of Willis that the frequency of hepatic metastases was due to poor hepatic oxygenation and of Haddow that some more specific factor, such as a "growth promoting substance," may be concerned.

Zeidman and associates have shown that tumor cells are capable of passing through the liver. The threefold increase in incidence and size of metastases observed if tumor cells were injected after caval constriction may in part be due to a trapping of cells in the liver. This explanation is less reasonable in our experiments, for similar results were obtained when cells were injected 10 minutes or as long as 2 days prior to constriction.

Our observations that the blood supply to hepatic tumors is arterial confirm those of others. Previously we reported (6) similar hemodynamics in the cirrhotic liver with artificially induced hepatic metastases. Wright, in 1937, was one of the first to demonstrate that when a fibrovascular stroma develops in secondary carcinoma, the afferent blood supply is from the hepatic artery. Subsequently, Mann, Wakim, and Baggenstoss demonstrated that the vascular supply to a primary carcinoma of the liver following hemochromatosis is predominantly arterial, and Breedis and Young reported similar findings in liver tumors of various animals and secondary tumors of liver in man. More recently, Murthy studied the vascular pattern of liver tumors in rats induced by the azo dye butter yellow and concluded that this tumor depended on the hepatic artery, and not the portal vein, for its blood supply. We have also observed that when tumor cells are injected into the liver by way of the hepatic artery rather than the portal vein, the blood supply to the metastatic growths was the same as when tumor cells arrived by way of the portal vein. All of these findings suggest that the use of cancer chemotherapeutic agents, both in man and in animal, via the portal vein is ill-considered, for they would bypass the neoplasms and would only come in contact with them after recirculation.

In view of the fact that the tumors have an arterial blood supply, it might well have been anticipated that hepatic artery ligation or hepatic congestion with its consequent stagnation and hypoxia might have resulted in inhibition or regression of metastatic growth rather than the observed enhancement. Indeed, Markowitz in 1952 suggested therapeutic ligation of the hepatic artery in the management of hepatic neoplasms. Prior to this, Breedis and Young tested the possibility of tumor regression in a small series of rabbits with carcinoma by hepatic artery ligation. Regression did not occur, and they attributed this to the fact that the arterial supply to the neoplasms was not completely eliminated inasmuch as collaterals derived from diaphragmatic and other vessels were still present. In our experiments, if shortly after hepatic artery ligation the portal vein was occluded and India ink injection studies were performed, a complete absence of arterial blood supply to the liver was demonstrated. When animals were similarly injected 2 weeks after hepatic artery ligation, only a small amount of ink was observed to get into the liver through a sparse number of collaterals. Therefore, in spite of the absence of significant arterial collaterals, inhibition of tumor was not observed. To effect regression, complete devascularization is required, as has been recently demonstrated by Kraus and Beltran who ligated all structures in the portal radicle to a liver lobe containing tumor.

SUMMARY

To obtain information relative to the influence of blood and oxygen supply of the liver upon the take and growth of artificially induced hepatic metastases, hepatic blood flow has been altered by caval constriction, hepatic artery ligation, and portacaval shunt.

Partial caval occlusion with resultant hepatic congestion when performed just prior to or as long as 2 days after tumor cell inoculation markedly increased both the incidence of animals demonstrating metastases and the size of the tumors observed. Similar augmentation was seen in animals whose hepatic arteries were ligated 3 days before or shortly after intraportal inoculation of tumor cells. Portacaval shunt, though decreasing hepatic blood flow, produced no such effect.

While no evidence is presented to affirm or deny that the reduction in hepatic oxygen supply specifically affects the tumor cell so that it "takes" and grows more readily, it is demonstrated that all of the procedures used to alter the hepatic blood and oxygen supply affected the "soil" by producing liver injury. Evidence would suggest that the concomitant hepatic regenerative process in response to the damage, possibly through an elaborated humoral factor, enhances hepatic metastases. The failure of metastatic augmentation and of liver regeneration to occur after portacaval shunt would lend support to the absence of a growth-promoting agent in such animals.

Injection studies demonstrating the arterial blood supply of hepatic neoplasms confirm the findings of others and suggest that the administration of chemotherapeutic agents to destroy hepatic tumors via the portal vein is ill considered.

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THE RESPONSE OF THE CANINE LIVER TO ANAEROBIC METABOLISM INDUCED BY HEMORRHAGIC SHOCK

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IT HAS BEEN KNOWN for many years that hemorrhagic shock produces hypoxia in tissues. Associated with this is a depletion of glycogen in liver and muscle, a late hypoglycemia, and an eventual exhaustion of the substances required for biologic energy transformations. It has been suggested by Le Page that this depletion of high energy substances, especially high energy phosphates, results in failure of the medullary centers and death. During the phase of progressive hypoxia, there is, therefore, an attempt to conserve energy and to utilize a lesser amount of oxygen by shifting to anaerobic carbohydrate metabolism. The degree to which the body is able to conserve its high energy stores during diminished tissue oxygen supply is an important factor in preserving life. The product of anaerobic carbohydrate metabolism, however, is lactic acid and it is well known that a rise in lactate content of the blood occurs during the course of hemorrhagic shock. This increase in lactate contributes significantly to the development of an uncompensated metabolic acidosis which may further threaten life. Thus, the by-product of an attempt by the body to preserve life acts deleteriously in itself. This investigation was undertaken to measure the degree of anaerobic metabolism during the course of hemorrhagic shock and to determine the role of the liver in contributing to or clearing lactate from the blood.

The lactate-pyruvate ratio has been utilized as a measurement of the sharper rise in lactate than pyruvate during hemorrhagic shock. A rise of lactate in the blood, however, is not exclusively a function of anaerobic metabolism. When pyruvate is converted to lactate, diphosphopyridine nucleotide (DPN) is converted from its reduced to its oxygenated form. This is known as the lactic dehydrogenase (LDH) system and is expressed:

$$\text{(1) Pyruvate} + \text{DPNH}_2 \overset{\text{LDH}}{\rightleftharpoons} \text{Lactate} + \text{DPN}.$$

When the same equation is expressed in its mass action form:

$$\text{(2) [Lactate]} = \text{[Pyruvate]} \times K \frac{[\text{DPNH}_2]}{[\text{DPN}]},$$

it becomes apparent that the concentration of lactate at any given moment is dependent upon the concentration of pyruvate and the adequacy of oxygen supply which is reflected by $K\frac{[\text{DPNH}_2]}{[\text{DPN}]}$, Thus, neither the concentration of lactate nor the lactate-pyruvate ratio is an accurate expression of the relationship between the metabolism of a tissue and its oxygen supply. Changes in lactate and pyruvate concentrations in the blood in the absence of hypoxia have been demonstrated by Huckabee during hyperventilation or when *p*H or blood glucose concentrations are altered (8). This author has suggested that the term "excess lactate" be used when discussing the quantitative relationship between lactate and pyruvate. Excess lactate represents that lactate which accumulates as a result of anaerobic metabolism. Using the mass action equation given before, Huckabee has derived the following formula:

$$\text{(3) } XL = (L_n - L_o) - (P_n - P_o)\ (L_o/P_o),$$

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TABLE I.—RESULTS

Exp. No.	*Time, mins.*	*B.P. mm. Hg*	*H.B.F. ml./kgm./min.*	*Excess lactate mM./L. Art.*	*P.V.*	*H.V.*	*A.M.R. Art.–H.V.*
1	0	140	76	0	0.2	−0.8	−17
	45	50	71	0.2	0.9	−0.5	−10
2	0	110	—	0	0.4	−0.2	−4
	50	50	—	0.1	0.2	−0.4	−4
3	0	140	—	0	—	—	—
	40	70	—	0.4	0.8	0.1	—
	80	50	—	1.0	1.9	1.2	—
	120	40	—	1.9	1.9	1.7	—
4	0	120	61	0	0.1	−0.4	−10
	40	50	—	0.4	1.1	−0.5	—
	100	40	31	0.3	0.9	−0.4	—
	130	30	—	4.0	4.3	6.8	36
5	0	80	41	0	0.8	0	—
	5	50	—	0.5	0.9	0.8	—
	38	20	—	1.9	3.0	4.0	—
	50	15	—	4.5	4.9	6.0	—
	63	65	52	3.3	4.2	4.2	—
6	0	85	42	0	0.3	−1.1	—
	15	40	30	−0.2	0.5	−0.9	—
	30	15	—	0.2	0.8	0.1	—
	60	90	58	0	1.0	−0.6	—
7	0	80	50	0	0.1	−0.3	—
	25	30	—	−0.2	0.1	−0.3	—
	45	30	—	0.1	0.6	0.5	—
	90	60	33	0.2	0.5	−0.2	—
8	0	90	—	0	—	—	—
	40	70	45	0.9	0.8	0.5	− 8.2
	85	20	—	1.8	2.8	2.2	4.0
	160	100	74	3.1	3.1	2.6	−14.7
9	0	130	—	0	—	—	—
	40	100	—	1.0	1.9	0.3	− 8.1
	50	40	—	2.1	3.5	3.6	7.2
	62	20	—	5.6	5.2	6.9	8.5
	70	0	—	4.2	8.4	8.9	25.8

where XL is the excess lactate, L_o and P_o are the initial concentrations of lactate and pyruvate measured in arterial blood during a nonhypoxic period, and L_n and P_n are the concentrations of lactate and pyruvate at any later time. All determinations are expressed in millimols per liter. In Figure 1 are illustrated 9 hypothetical combinations of lactate and pyruvate determinations. The lack of correlation between lactate-pyruvate ratios and excess lactate calculations is demonstrated.

Excess lactate may be calculated for arterial samples of blood in which case the result indicates the rate of accumulation or removal of the excess lactate of the whole body as conditions are varied. By utilizing the venoarterial differences in measured lactate and pyruvate, the equation may be adapted in order to study the change in excess lactate concentration as blood traverses a specific region of the body:

$$(4)\ XL = XL_v - XL_a = \left[(L_v - L_o) - (P_v - P_o)\left(\frac{L_o}{P_o}\right)\right] - \left[(L_a - L_o) - (P_a - P_o)\left(\frac{L_o}{P_o}\right)\right],$$

where L_v and P_v represent the concentrations of lactate and pyruvate in the venous blood draining the body area under consideration at a given time. L_a and P_a refer to arterial concentrations of lactate and pyruvate at the same time, while L_o and P_o are the initial lactate and pyruvate concentrations in arterial blood (see formula 3).

What is actually determined in using these formulas is the state of oxidation of DPN or the balance between the rate of cellular oxidation and effective rate of oxygen supply. Thus, the rate of excess lactate formation is proportional to the rate of anaerobic metabolism. In addition, the rate of development of oxygen debt may be expressed as a fraction (per cent AMR) of the total metabolic rate:

$$(5)\ \text{Per cent AMR} = \frac{K_{o_2}(XL_v - XL_a)}{(Ca_{o_2} - Cv_{o_2}) + K_{o_2}(XL_v - XL_a)}$$

where per cent AMR is the percentage anaerobic metabolic rate, $(Ca_{o_2}\text{-}Cv_{o_2})$ is the arteriovenous difference in oxygen content of the blood expressed in milliliters per liter and K_{o_2} is the oxygen equivalent of XL (11.2 milliliters oxygen per millimol XL) as shown by Huckabee (9). When excess lactate is removed by an organ, the following formula is used:

$$\text{Per cent AMR} = \frac{K_{o_2}(XL_v - XL_a)}{Ca_{o_2} - Cv_{o_2}}$$

The value for per cent AMR becomes negative and indicates the rate of diminution of O_2 debt expressed as a fraction of the total metabolic rate.

The work of Huckabee, allowing a quantitative calculation of that lactate produced by anaerobic metabolism (excess lactate), forms the basis of the investigation. Using these formulas it should be possible to measure the change in excess lactate and hence

the percentage of anaerobic metabolism in any area of the body from which representative blood samples may be obtained.

MATERIALS AND METHODS

Nine adult mongrel dogs were used in these experiments. At an initial operation, a common hepatic vein was created from the inferior vena cava between the liver and the heart, using a method previously employed by us (2). At the same time, polyethylene catheters were introduced into the common hepatic vein and the portal vein. These catheters were filled with heparin-saline solution and their distal tips heat-sealed and buried in the subcutaneous tissues. After a lapse of several weeks, collateral circulation had developed between the inferior vena cava caudad to its divided stump and the superior vena cava. The common hepatic vein then contained hepatic venous blood collected from all lobes of the liver. The animals were reoperated upon at this time, using sodium pentobarbital anesthesia. The distal ends of the previously implanted catheters were dissected free from the subcutaneous tissues and their sealed tips were cut. A third catheter was placed in the femoral artery in order to record arterial blood pressure and to allow sampling of arterial blood. A very slow saline infusion maintained the patency of the catheters during the course of the experiment. Two milligrams of heparin per kilogram of body weight were given intravenously. The positions of the catheters were ascertained after a rapid injection of a small quantity of indocyanine dye into the portal catheter. The catheter from the common hepatic vein was connected to a densitometer cuvette and oscilloscope. Rapid appearance of the dye (7 to 10 seconds) and a sharply rising peak indicated that both catheters were in the correct positions. The validity of this was assured by the previous performance of over 70 hepatic blood flow measurements using this technique (1). Samples of arterial, hepatic venous, and portal venous blood were drawn from the 3 catheters. Blood was then rapidly withdrawn—

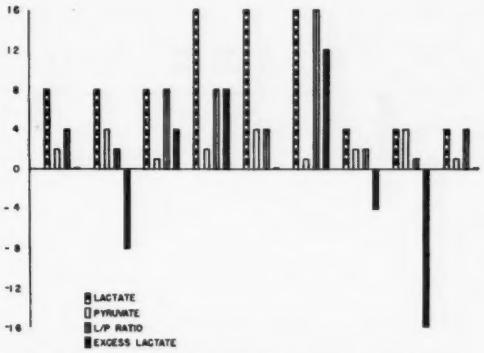

FIG. 1. Nine combinations of lactate and pyruvate content of the blood illustrate the lack of correlation between the lactate-pyruvate ratio and the calculated excess lactate.

in approximately 2 minutes—from the common hepatic vein until the blood pressure fell to a predetermined level (Table I). In 7 of the animals subsequent bleedings reduced the blood pressure further, the lowest level measured in any animal being 15 millimeters of mercury. In experiment 9, after the last hemorrhage the blood pressure became unobtainable and the heart began to fibrillate. The total amount of blood withdrawn varied between 1.5 and 4.5 per cent of body weight. In 4 cases (experiments 5, 6, 7, and 8) the animals were transfused with their own shed blood. In other experiments, the animals were bled progressively until death. During the course of hemorrhage and after transfusion, blood samples were again drawn from the 3 catheters. Hepatic blood flow determinations were made at intervals during 6 experiments.

Lactates were determined according to the method of Barker and Summerson, as modified by Huckabee (7), pyruvates according to the method of Friedemann and Haugen. Blood proteins were precipitated by chilled trichloracetic acid within 30 seconds of drawing the sample. All determinations were done in triplicate. When known amounts of lactate were added to blood, we recovered an average of 103 per cent ± 3 per cent over a wide range of values. Duplicate determinations of lactate

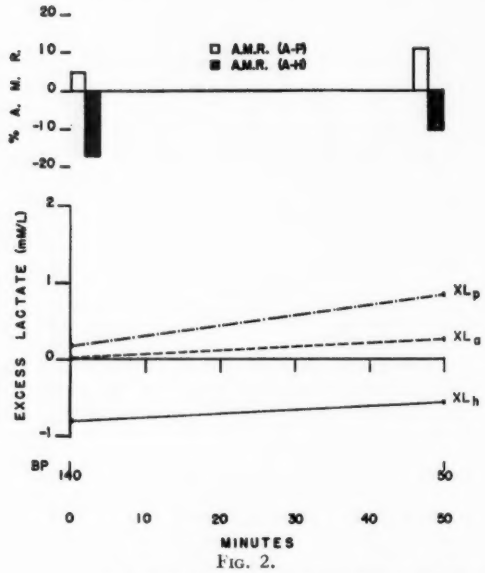

FIG. 2.

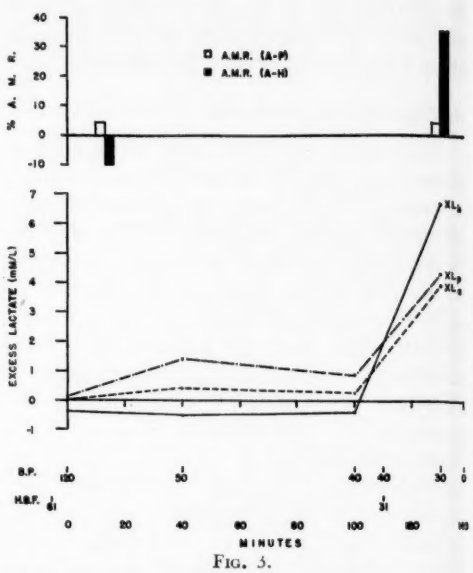

FIG. 3.

FIG. 2. Experiment 1. Excess lactate (XL) in arterial (a), portal venous (p), and common hepatic venous (h) blood before and after hemorrhage. The arterial blood pressure has been reduced to 50 millimeters of mercury for 50 minutes. The liver continues to remove excess lactate. The anaerobic metabolic rate (AMR) across the arterioportal venous gradient (A-P) rises. At the same time, there is a negative anaerobic metabolic rate across an arterial-hepatic venous gradient (A-H).

FIG. 3. Experiment 4. Arterial blood pressure was reduced to a lower level than in the experiment shown in Figure 2. Hepatic blood flow (HBF) fell to 50 per cent of prehemorrhage level. The liver removed excess lactate until late in the course of shock, then shifted to a predominantly anaerobic metabolism and contributed excess lactate to the blood.

content of the blood were always within 0.2 millimols per liter. Duplicate determinations of pyruvate in blood checked to within 0.04 millimols per liter.

Oxygen content of blood was measured in 5 experiments according to the method of Van Slyke and Neill.

RESULTS

Excess lactates and anaerobic metabolic rates calculated from the data in each experiment are given in Table I. As the blood pressure fell, excess lactate progressively increased in the arterial blood. In the hepatic venous excess lactate column, negative values indicate removal of excess lactate by the liver, while positive values indicate accumulation. In all cases, as hemorrhage and hypotension developed, the low excess lactate values rose, although the change in experiment 2 is probably not significant. During the earlier period of hypotension, the excess lactate values in the blood withdrawn from the common hepatic vein were less than those in the arterial or portal venous samples with the exception of experiment 5. With the exception of experiment 6, during severe hypotension the excess lactate in the common hepatic vein rose above that of the portal vein or artery. In 3 of 4 experiments (No. 6, 7, and 8) in which the animals were transfused with their own shed blood, the excess lactate in the common hepatic vein fell more than the excess lactate in either the arterial or portal venous samples.

The rate of hepatic blood flow decreased as the mean arterial blood pressure fell. The arteriovenous differences in oxygen content rose during the course of hemorrhagic shock in the 5 experiments in which oxygen content

of the blood samples was determined. The rate of anaerobic metabolism (per cent AMR) was calculated in these experiments. In Table I, A.M.R. Art.-HV indicates the rate of anaerobic metabolism in the tissues drained by the common hepatic vein. In all cases, there was a negative rate at normotensive levels. In experiments 1 and 2, the anaerobic metabolic rate was negative even when a mean arterial blood pressure of 50 millimeters of mercury had been maintained for 45 and 50 minutes respectively. In experiments 8 and 9, the anaerobic metabolic rate rose progressively. This continued until the death of the animal in experiment 9, but was reversed by transfusion and restoration of blood pressure in experiment 8.

Figure 2 illustrates the results of experiment 1. The rate of hepatic blood flow in the animal was high initially and did not change significantly after hemorrhage. The arterial-hepatic venous oxygen difference rose from 5.5 initially to 8.4 volumes per cent after 45 minutes of reduced blood pressure. There was a slight rise in excess lactate in all 3 blood samples at this time. Nevertheless, the excess lactate in the hepatic vein remained a negative value, below that of either the arterial or portal venous sample.

Figure 3 illustrates experiment 4 in which the mean arterial pressure was reduced somewhat lower and shock levels were maintained for longer than in experiment 1. Hepatic blood flow fell to 50 per cent of the initial value. The arterial-hepatic venous oxygen difference at conclusion of the experiment, with a blood pressure of 30 millimeters of mercury, was only 1.1 volume per cent higher than the prehemorrhage oxygen difference. The second hepatic blood flow was measured 20 minutes before the final determinations of oxygen content. Therefore, splanchnic oxygen consumption could not be calculated at the time the last blood samples were obtained. However, there is little doubt that there was a severe drop in oxygen consumption at this stage of the experiment. The liver continued to remove excess lactate for 100 minutes after the drop in blood pressure to 50 millimeters of mercury or lower. The liver then shifted to a predominantly anaerobic metabolism and contributed excess lactate to the general circulation, the amount in the common hepatic vein exceeding that in either the arterial or portal venous blood.

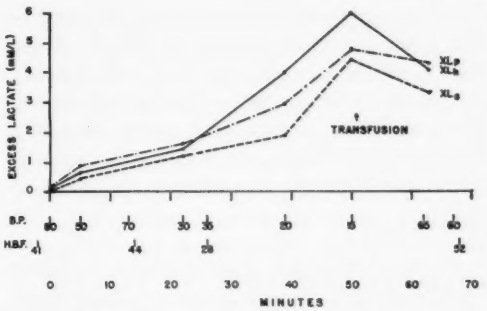

FIG. 4. Experiment 5. This animal was in poor condition at the onset of the experiment and the initial mean arterial blood pressure was only 80 millimeters of mercury. At no time was there a negative value for excess lactate in the common hepatic venous blood. After hemorrhage, excess lactate in common hepatic venous blood exceeded that in arterial or portal venous blood. Transfusion of shed blood caused the excess lactate content of hepatic venous blood to fall more rapidly than that of arterial or portal venous blood.

A different pattern, noted at the onset of experiment 5, is shown in Figure 4. The initial arterial blood pressure was only 80 millimeters of mercury. Hepatic blood flow was 41 milliliters per kilogram per minute, lower than an average of 56 milliliters per kilogram per minute previously obtained by us for dogs under these conditions (1). Before the induction of anesthesia, this animal was noted to be less alert and to have a poorer general appearance than the other dogs. At no time was there a negative value for excess lactate in the blood withdrawn from the common hepatic vein. During the course of the experiment, the excess lactate in the 3 specimens rose in a parallel fashion until an arterial blood pressure of 30 millimeters of mercury was reached. The excess lactate in the common hepatic venous blood then rose more sharply than the excess lactate in the arterial or portal venous blood. Transfusion of the shed blood resulted in a partial resto-

ration of arterial blood pressure and a considerable increase in hepatic blood flow. Excess lactate in all 3 samples decreased, that in the hepatic venous sample somewhat more than the others, indicating that the liver was recovering its ability to remove excess lactate from the general circulation.

DISCUSSION

Engel and Russell and his associates have indicated that changes in metabolism of the peripheral tissues are responsible for the alterations in blood lactate and pyruvate and that the liver does not participate prominently in these alterations. Our previous studies of the role of the canine liver during hemorrhagic shock (3) revealed that a reduction in arterial blood pressure to below 40 millimeters of mercury, a fall in hepatic blood flow to approximately 50 per cent of the control values, and a fall in oxygen content of the hepatic venous blood to less than 4 volumes per cent are necessary to reduce oxygen consumption of the tissues drained by the common hepatic vein. One would not expect that the liver would shift from aerobic to anaerobic metabolism unless the oxygen consumption were reduced and hence the conditions mentioned fulfilled.

The data obtained in this study confirm this prediction. In every animal, as mean arterial blood pressure was reduced, there was a marked drop in hepatic venous oxygen content and hepatic blood flow. Excess lactate rose in arterial and portal venous samples during the progression of hemorrhagic shock. The liver, however, continued to remove excess lactate until very low mean arterial blood pressures were attained. At this point, the excess lactate in the hepatic venous blood rose sharply and exceeded that in the arterial or portal venous blood. The complexity of performing hepatic blood flow determinations and simultaneously removing blood samples for analysis did not permit accurate calculation of splanchnic oxygen consumption in these experiments. The hepatic blood flow was always measured a few moments before or after samples were removed for oxygen content or lactate and pyruvate determinations. Our data in these experiments revealed that the same conditions of mean arterial blood pressure, hepatic venous oxygen content and arterial-hepatic venous difference in oxygen content prevailed as in the previously reported experiments. It is reasonable, therefore, to assume that the rise in hepatic venous excess lactate occurred only after a drop in splanchnic oxygen consumption. Thus, the liver, in shifting to anaerobic metabolism, contributes excess lactate to the blood rather than removing it. The calculated anaerobic metabolic rates confirm this assumption.

Transfusion of the shed blood reduced excess lactate in 3 of 4 experiments. In 2 of 4 experiments, the excess lactate in the hepatic venous sample returned to a negative value. In experiment 5, excess lactate was reduced following transfusion, the greatest reduction occurring in the hepatic venous sample. This indicated that, while not enough time had elapsed to allow removal of the products of anaerobic metabolism, the liver was resuming its function of clearing excess lactate from the general circulation. Experiment 8 was the only example in which excess lactate continued to rise in all samples despite restoration of normal arterial blood pressure after transfusion. This animal received a transfusion of stored homologous canine blood which is known to have an elevated lactate content and which probably accounted for the continued rise in excess lactate. In addition, the dog died shortly after these posttransfusion samples were obtained, suggesting the possibility of an incompatibility reaction. Nevertheless, the rise in oxygen content following transfusion resulted in a return to a negative anaerobic metabolic rate across the arterial-hepatic venous gradient.

Lactate and pyruvate concentrations were not determined in the blood before transfusion. Therefore, a criticism of the

results of the experiments could be that the fall in excess lactate following transfusion in 3 of 4 experiments was related to a dilution effect caused by the transfused blood. However, the fact that the excess lactate fell more sharply in hepatic venous blood than in arterial or portal venous blood indicated that the liver had returned to aerobic metabolism and was removing excess lactate.

The results of these experiments, therefore, are contrary to the findings of Engel that the liver does not play an important role in the alterations due to anaerobic metabolism. Our data indicate that the liver removes excess lactate until late in the course of shock when there is no longer sufficient oxygen available to permit this organ to maintain an aerobic form of metabolism. Only then does it contribute excess lactate to the general circulation. Thus, the body, conserving energy, shifts to a predominantly anaerobic metabolism during the course of hemorrhagic shock. At the same time, however, the liver is able to protect the organism against the metabolic acidosis resulting from lactic acid production. Finally, however, this protective mechanism fails, and the liver also contributes to the progressive acidosis.

It is interesting to speculate upon this protective function when the liver is diseased or when, during the course of an operation, the portal vein or thoracic aorta is temporarily occluded. Furthermore, the effect of hypothermia upon the production of excess lactate in the periphery and its removal by the liver is not well understood. These clinical situations are currently being studied in this laboratory. In addition, the degree to which rises in lactate, pyruvate, and excess lactate contribute to the development of metabolic acidosis is being investigated.

SUMMARY

1. The lack of correlation between blood lactate and pyruvate levels, the lactate-pyruvate ratio, and the degree of anaerobic metabolism is demonstrated. Excess lactate, as defined by Huckabee, includes only that lactate produced by anaerobic metabolism. The formulas for the calculation of excess lactate and the anaerobic metabolic rate are presented. These determinations have been applied to assess the role of the liver in hemorrhagic shock.

2. When dogs were rapidly bled, hepatic blood flow and the oxygen content of hepatic venous blood fell. The arterial-hepatic venous difference in oxygen content rose until late in the course of hemorrhagic shock.

3. Excess lactate in arterial and portal venous blood rose as the dogs were bled. At normotensive levels and until mean arterial blood pressure fell to 40 millimeters of mercury or below, excess lactate was almost always lower in hepatic venous blood than in arterial or portal venous blood.

4. During profound shock, excess lactate in hepatic venous blood exceeded that in arterial or portal venous blood.

5. It is concluded that the liver is able to clear the products of anaerobic metabolism (excess lactate) from the arterial and portal venous blood until the animal is in deep shock. The liver itself then shifts to a predominantly anaerobic metabolism.

6. This conclusion is confirmed when the anaerobic metabolic rate across an arterial-hepatic venous gradient is calculated.

7. Following transfusion, the liver recovers its ability to clear excess lactate and shifts to a more predominantly aerobic metabolism.

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UROLOGIC PROBLEMS IN CARCINOMA OF THE CERVIX

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THE HIGH INCIDENCE of urinary tract involvement in the natural growth processes of carcinoma of the cervix and the frequency of urologic complications after surgical measures, irradiation, or both, directed to eradication of the disease, have long been recognized. When both measures of therapy have been employed the problems are considerably augmented. Radical and superradical surgical procedures have logically resulted in the increase of this incidence. It is well authenticated that impairment of renal function due to ureteral obstruction with attendant pyelonephritis and uremia is the most common cause of death in the victims of this disease. An opportunity to assess and manage, from the urologic viewpoint, both before and after treatment, approximately 1,800 women suffering with malignant lesions of the cervix at the Pondville State Cancer Hospital of the Massachusetts Department of Public Health has resulted in many indelible impressions and valid conclusions.

The progress in irradiation therapy and the dramatic advances in surgical management have significantly affected the picture of the urinary tract. It cannot be denied that except in the well organized clinics the services of the urologist are in most instances requested only when the gynecologist is faced with a perplexing problem. The all too frequent laissez-faire attitude should be discouraged, as failure to investigate and adequately manage the urinary tract may result in needless morbidity and irreversible renal damage which may spell defeat for the surgeon and dire tragedy to the patient.

When a diagnosis of carcinoma of the cervix is made, an evaluation of the urinary tract should be carried out to determine the status of the bladder, the presence or absence of ureteral obstruction, and the degree of renal impairment, if present. This information can readily be obtained by determination of renal values, careful urinalysis, cystoscopy, and intravenous urography. When findings are negative or inconclusive a baseline of information is obtained for future comparisons.

Bladder disturbances will depend on the extent of the lesion in the cervix as well as the type and character of the growth. There are three recognized types, proliferative, ulcerative, and invertive. The proliferative lesion, which grows outward from the cervix and is described as outcropping, fungating, or cauliflower-like, is less prone to invade the bladder directly. The ulcerative type leads to destruction of the cervix and has a high incidence of vesical invasion. The invertive or infiltrating type is predominantly endocervical, and parametrial involvement with ureteral occlusion occurs frequently.

The earliest indication of bladder disturbances is the effect of extravesical pressure which presents itself on cystoscopy as a relatively uniform elevation of the proximal trigone and distal posterior wall with normal mucosa and unaffected by distention. As the malignant process advances toward the bladder or actually invades it, localized areas of congestion with submucosal hemorrhage and later edema follow. We are of the opinion that bullous edema associated with extravesical pressure is indicative of carcinoma in the bladder wall beneath. Further invasion may lead to submucous nodules or definite tumor projecting into the bladder cavity with or without ulceration and distortion. Biopsy may be informative but is not ordinarily indicated.

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On the other hand, the bladder may be absolutely innocent in the presence of advanced disease in the cervix with parametrial involvement and ureteral occlusion. The end result of the process in the bladder lies in fistula formation which may be so minute as to be unrecognized.

An important phase in the subject of bladder complications is the condition which may result from treatment of the disease rather than from the disease itself, the so-called remote radiation effect, which may give rise to diagnostic confusion if the surgeon is not aware of its incidence. The incidence of this problem has markedly diminished at the Pondville Hospital in recent years. The type and degree of the reaction will vary with the proximity of the primary disease to the bladder, the presence or absence of vesical involvement by the malignant process, and the type and degree of radiation. These late or remote effects present themselves months or even years after therapy. In our clinic the average length of time from irradiation to the onset of symptoms was 27 months. The late effects result from vascular changes varying from mild endarteritis to complete ischemic necrosis. The bladder findings may be pathognomonic, revealing a sharply defined area of central slough surrounded by a zone of hyperemia and edema located in the midline posterior wall just above the trigone. However, the picture may vary from a small area of hyperemia and telangiectasis to definite slough and ulceration and even fistula. It should be emphasized that under such circumstances the fistula may be the result of disease rather than radiation. The clinical distinction between this entity and actual cancerous invasion is frequently difficult. A history of radium treatment of the cervix followed by a long interval before the advent of hematuria—the most frequent presenting sign—and the appearance of the lesion is highly suggestive of late radiation reaction. Correlation with the status of the disease in the cervix is fundamental. Periodic bladder inspection to determine regression or progression should be carried out. The prognosis is excellent with regard to healing, but in practically all cases there is a permanent scar with surrounding telangiectasis. There may be an early or acute radiation reaction which occurs at the height of the effect in the cervix and is manifested by symptoms of frequency, urgency, dysuria, and hematuria which usually subsides but may occasionally advance to ulceration or even fistula formation.

The proximity of the distal ureter to the broad ligament and anterior vaginal wall predisposes it to involvement as the disease in the cervix progresses. Occlusion of the ureters, partial or complete, unilateral or bilateral, with the inevitable deteriorative changes above the obstruction in women with carcinoma of the cervix as a direct result of the natural growth of the disease or as a direct complication of therapy, presents a real problem to the gynecologist and to the urologist who may be consulted. Early recognition of this complication and its proper management are fundamental. It is only by a thorough urologic evaluation before therapy is instituted that ureteral involvement will be detected. It may be stated without hesitation that ureteral involvement is a grave prognostic sign and may be assumed to be due to malignant disease until otherwise proved. Experience has shown that it is important not to be led astray by the absence of renal pain and tenderness, as profound irreversible renal damage may occur without local signs and symptoms. The silent death of a kidney is not uncommon in carcinoma of the cervix. This occurrence has been repeatedly demonstrated in the Pondville Hospital. Ureteral instrumentation has confirmed the usual site of occlusion to be from 4 to 6 centimeters above the orifice. This level is the result of the anatomic position of the ureter beneath the broad ligament and close to the cervix and upper part of the vagina. In fact, ureteral obstruction may take place in the absence of parametrial spread. The encroaching tumor itself is the recognized

factor in ureteral obstruction. There may be a constricting effect from edema or an inflammatory process adjacent to the growth and, as the malignant process advances, actual compression or direct invasion of the ureter follows. Edema after irradiation may precipitate complete obstruction where partial occlusion had previously existed, but it is highly probable that when ureteral obstruction is progressive after the immediate irradiation effects have subsided it is indicative of active disease in this area. Obstruction of the normal ureter is rare after this therapy.

The management of the ureteral complications in carcinoma of the cervix presents multiple problems, and each woman must be meticulously individualized. No routine program may be planned. One must decide whether the ureteral disease is the result of the natural progress of the malignant process or the effect of treatment, irradiation, operation, or both. When noted prior to treatment a policy of judicious observation may be warranted, particularly when dealing with unilateral obstruction without infection or pain and when investigation suggests a functionless kidney on the involved side and a normal contralateral upper urinary tract. When ureteral or renal pain is present, simple ureteral dilatation may result in transient relief. It should be noted, with reference to ureteral dilatation, that a ureter which has lost its tone and contractility because of stenosis of some duration and is surrounded or actually invaded by cancer cannot be expected to resume normal drainage after the mere passage of a catheter, especially when a relatively large segment of the ureter is involved. In many cases, ureteral dilatation is technically impossible because of vesical distortion or involvement.

Diversion of the urinary stream by nephrostomy may be indicated when pain unrelieved by simpler measures, sepsis within the blocked kidney, or signs of uremia with oliguria or anuria are encountered. It can be performed with safety and without shock in even the profoundly sick patient. We do not advocate, however, the procedure in the presence of extensive irreversible malignant disease and in profound uremia, unless there is a reasonable life expectancy. Occasionally a nephrectomy is performed in patients with carcinoma of the cervix if the integrity of the opposite kidney has been established. In most instances when indicated preliminary nephrostomy has been resorted to, which enables one to watch the remaining kidney for evidences of damage. If after a reasonable period its integrity has been confirmed the diseased kidney may be sacrificed. In the care of these patients one must obviously be influenced at all times by the condition of the patient, extent and activity of the disease, probable life expectancy, prognosis for cure, and renal status.

Radical total hysterectomy with bilateral lymphadenectomy is a well recognized method of eradicating cancer of the cervix and, when adequately performed, disturbances of bladder function are almost inevitable and the incidence of ureteral damage is significant. Neurogenic vesical dysfunction is a common occurrence after such an operation and, unless properly interpreted and intelligently managed, a permanently functionless organ with profound damage to the kidneys may follow. When complete surgical removal of cancer deep in the pelvis is carried out the continuity of many nerve bundles is interrupted or ganglia are excised. On the other hand, such dysfunction is not a universal finding even after really radical pelvic operations and, even if present, may be transient. As to the reasons for such functional variation, McCrea and Kimmel have demonstrated an accessory nerve distribution to the bladder which lies laterally in the endopelvic fascia independent of the main chain of the pelvic plexus and they believe that these nerves are capable of maintaining bladder function when the pelvic plexus is irreparably damaged. The postoperative care of the handicapped bladder is a prime requisite. At the present time at the Pondville Hospital,

Foley catheter drainage is instituted immediately postoperatively. Drainage is continued for 6 to 8 weeks after operation, at the end of which time the patient returns to the hospital and remains overnight. The catheter is removed immediately, and when and if she voids spontaneously a determination of residual urine is made and if emptying is not satisfactory she is discharged and further drainage instituted. A desire to void during drainage is suggestive of returning function. This program has been highly satisfactory. The secondary objective of this regimen is to minimize the incidence of ureterovaginal fistula. It was noted that there was a definite incidence of fistula development between the eighth and fourteenth days after operation. Meigs theorized that when overdistention of the bladder occurred the ureter may be lifted from its new bed on the pelvic floor and that the new and delicate blood supply may be destroyed with consequent necrosis and sloughing of the ureter. Smith has suggested leaving ureteral catheters in situ after operation when, in his opinion, the degree of angulation threatens interference with ureteral drainage.

The threat to ureteral integrity in the surgical treatment is well recognized. Among those who have attained technical proficiency, direct ureteral damage infrequently takes place, but in spite of meticulous precaution it does occur. Any detailed discussion of the types of injury to which the ureter is exposed such as ligation, crushing, angulation, resection, incision, and perforation would be superfluous. Sloughing due to interference with the blood supply of the distal ureter is the most significant factor in fistula formation after the radical surgical technique. Ulfelder believes that it seems impossible to reduce the incidence of ureterovaginal fistula below 5 to 8 per cent when operation is adequate. It is reasonable to state that in the radical surgical attack on carcinoma of the cervix interference with ureteral integrity is at times unavoidable and that when the incidence is negligible it may be predicated that the operation was not as extensive or as thorough as it should have been. A precise knowledge of the anatomy of the ureter including its blood and nerve supply, its course, and its possible anomalies is fundamental, as well as an appreciation of the changes which may result from malignant degeneration, irradiation, inflammatory reaction, and previous surgical intervention. In radical hysterectomy the ureter is completely mobilized and closely stripped of its periureteral connective tissue and is returned to an oozing retroperitoneal bed. The ureter becomes fragile and edematous and may be seen stretching across its bed like a clothes line or telephone wire. Meigs emphasizes the importance of preserving the longitudinal ureteral vessels and leaving the ureter attached to the peritoneum, if possible. Operation must be adequate but the blood supply should be protected.

Hydroureter and hydronephrosis are the usual sequelae of the Wertheim operation. This is the rule rather than the exception and has been demonstrated regularly by postoperative urography in this clinic. In most instances regression takes place in the early postoperative period, but when this does not occur one must be on guard. When the obstructive changes are progressive, associated with signs and symptoms of sepsis, renal pain, abdominal distention, ileus, and loss of renal integrity, active intervention may be indicated. Vaginal drainage of urine will frequently herald the presence of a ureterovaginal fistula with improvement in symptoms due to drainage of previously trapped urine.

When damage to the ureter is recognized at the time of operation, immediate measures should be carried out to protect the kidney, minimize urinary extravasation, and forestall fistula formation. One cannot definitely anticipate sloughing, however. The method of repair varies with the site of injury—which in operations deep in the pelvis will obviously be the lower ureter—the type of injury, and the state of the traumatized

organ. End-to-end anastomosis of cut ends of the ureter is the elected procedure, although under such conditions it is unlikely to heal because of the unhealthy status of the distal segment. Transplantation of the proximal segment into the bladder is less hazardous and has been quite successful in this clinic. Ligation of the ureter above the site of injury is mentioned only to condemn it. It is generally known that unrecognized damage to the ureter may take place and that, in the absence of obstructive signs and symptoms, infection, and fistula formation, asymptomatic autonephrectomy may follow. Obviously, such an end result is an exception. Unrecognized ureteral injury or damage secondary to avascularization manifested in the late postoperative period are the situations in which the urologist is most frequently consulted. In general, the clinical manifestations are those of obstruction, infection, fistula, and occasionally extravasation. Meticulous individualization is mandatory. Whether one is dealing with unilateral or bilateral involvement is an important question. When unilateral disease has been confirmed, a policy of watchful waiting is warranted, as an obstructive process may regress and a fistula does heal spontaneously. Such a conservative program must be effected judiciously, and intervention must be carried out before profound irreversible renal damage takes place.

A complete urologic study is necessary in this group of patients, including a determination of renal values, intravenous urography, cystoscopy, and, when technically possible, ureteral instrumentation as well as ureterograms. Nephrostomy has a definite place in the management of postoperative ureteral problems. It is an operation devoid of shock and with practically no mortality and affords ideal drainage. There should be no hesitancy to perform it as a temporary or even occasionally permanent means of urinary diversion in the presence of a ureterovaginal fistula or ureteral obstruction. One is frequently dealing with an obstructed kidney and overwhelming sepsis, and after diversion there is relief of pain, decreased toxicity, and dramatic improvement in renal function. The future of the severely obstructed and infected kidney may be best protected by prompt drainage through nephrostomy, especially as a temporary diversion. Reconstructive measures can be safely carried out at some future date when general and local conditions are ideal, as indicated by the physical status of the patient, her improved renal values, plus her psychologic attitude toward further surgical treatment. If reparative operation is performed, the nephrostomy tube serves as a protective mechanism during the postoperative period and may be discontinued when and if normal ureteral drainage and continuity are established. The adjustment of patients to life with a nephrostomy has been excellent.

In a discussion of the surgical procedures available for ureteral disposition it must be again emphasized that the use of the distal ureter in any reparative or reconstructive procedure is not only inadvisable but may be technically impossible and therefore must be left out of any program. The lower ureter has lost its peristalsis and power of contractility as a result of fibrosis, depleted vascularization, and at times the effects of irradiation and is deeply embedded in dense scar tissue. In the presence of such an unhealthy distal segment, end-to-end ureteral anastomosis is not warranted. Reinsertion of the ureter into the dependent portion of the bladder is technically difficult as it requires undue tension on the anastomosis because of the shortened ureter. The ileal loop conduit may be warranted in the presence of bilateral ureteral disease, and is highly regarded as the diversion of choice under such conditions.

Implantation of the ureter into the upper portion of the bladder without tension has been very successful at the Pondville Hospital. The site of insertion will vary with the length of the proximal segment and should be as independent as is practically feasible. Landsteiner advocated the bladder pedicle ureterocystoplasty as an effective technique

to bridge the gap to the healthy proximal ureter, but it should not be carried out in the presence of a damaged or irradiated bladder.

The loss of a kidney by the victim of carcinoma of the cervix who has severe unilateral upper urinary tract disease as a result of the natural course of the carcinoma or after measures directed to its cure is at times good therapy. It must be emphasized, however, that removal is justified only when the total picture has conscientiously been considered and when the integrity of the opposite kidney has been confirmed and its expectancy of future function has been favorably established. The sacrifice of an irreversibly damaged kidney, which if not removed will spell increased suffering and morbidity, may not be too high a price to pay for cure of the malignant disease. Under proper conditions nephrectomy may be regarded as conservative treatment in a woman who has undergone operation for cervical cancer. Inexcusable and repeated attempts at so-called reconstructive operation may well be at times classified as meddlesome.

The disposition of the upper urinary tract in so-called superradical measures to eradicate advanced carcinoma of the cervix has presented intricate problems. In this hospital, in addition to the radical hysterectomy and lymphadenectomy, abdominal perineal resection of the rectum and cystectomy may be effected at one sitting. When the extent of the disease warrants its preservation, the bladder is not sacrificed, and in other instances the rectum is left intact. Fecal or urinary diversion or both must be carried out. The methods of procedure will depend on the status of the ureters and kidneys as well as on the choice of the individual surgeon. In the earlier years, the wet colostomy with transplantation of the ureters 6 to 8 centimeters above the stoma was the procedure of choice. This operation may be performed in the presence of moderately dilated ureters, as under these conditions reflux is no particular hazard. Fecal diversion through a transverse colostomy associated with urinary drainage through a sigmoid stoma has also been employed. The ileal loop conduit with a sigmoid colostomy has been a method of choice in recent years at this hospital. It must be recognized that patients eligible for superradical operation are in most instances in the advanced stages of cancer and a large percentage of them have had irradiation and a previously damaged upper urinary tract. If studies demonstrate bilateral renal damage with extreme hydroureter and hydronephrosis the kidneys may be best protected by skin ureterostomies. The technique is relatively simple and well tolerated and insures adequate drainage but is only rarely indicated. It is superfluous to add that one does not hesitate to provide drainage by nephrostomy at any time when there are evidences of poor drainage, intractable sepsis, and signs of progressive renal embarrassment. Lower nephron disease must be suspected in this group of patients in the early postoperative period when indications of anuria or oliguria are manifested. After such extensive operations vigorous measures must be carried out to prevent this not unusual sequela.

SUMMARY AND CONCLUSIONS

Urologic study prior to therapy should be routine in the woman with carcinoma of the cervix. Bladder and ureteral disease may result from the carcinoma itself or from the effects of treatment. Ureteral obstruction is a grave prognostic sign and may be assumed to be due to the malignant disease. The loss of a kidney by a victim of carcinoma of the cervix may not be too high a price to pay for cure. The management of the injured ureter after radical total hysterectomy is discussed.

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AN EXPERIMENTAL STUDY OF THE RADIOCARPAL JOINT BY ARTHROGRAPHY

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INJURIES of the wrist with negative roentgenray examination, the so called "derangement," "strain," or "sprain" of the wrist, are followed in many cases by different complaints. Clinically, one finds swelling around the joint, tenderness to palpation, limitation of movements, and pain upon attempted passive or active motion. When these findings remain for a prolonged period in spite of treatment, they are interpreted as traumatic synovitis or arthritis. In other cases, the swelling disappears in time, the movements of the joint improve considerably, and only rotatory movement is somewhat limited and accompanied by shooting pain. By more precise examination, tenderness on the ulnar side of the wrist joint can be observed. In such cases, an indefinite diagnosis is established, or a lesion of the triangular fibrocartilage is suspected.

Similar findings are known to occur also after injuries connected with fractures in the neighborhood of the wrist, usually of the radius. Sometimes the fracture—intra-articular or juxta-articular—takes a normal time to heal, movements become normal, and swelling disappears. In other cases, a similar fracture, or even a less severe one, results in many complaints and limitation of movement in spite of roentgenographic evidence of union.

The basic signs of these conditions (pain or limitation of motion or both) testify to wrist disability, the cause of which sometimes remains unclear. In our opinion, a reason other than the so called "traumatic synovitis," "sprain of the wrist," or the fracture itself has to be found in order to explain those signs.

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We present a technique of wrist joint arthrography and our impressions about this method as a means for further investigations of uncertain traumatic states.

ANATOMY

The subject of our study was the joint between the proximal row of the carpal bones and the articular surface of the radius in conjunction with the triangular fibrocartilage—the radiocarpal articulation or wrist joint. From the anatomic point of view this joint is a separate one. It is surrounded by a capsule and strengthened by the volar and dorsal radiocarpal and two collateral ligaments. The interosseous intercarpal ligament which covers the joint capsule on the distal wall of the wrist joint prevents the communication between this joint and the small joints in the proximal carpal row. According to Testut communication between the radiocarpal and the intercarpal joints is possible but is a rare condition. The communication to the radioulnar distal joint is prevented by the triangular fibrocartilage which with the lower extremity of the radius forms the proximal wall of the wrist joint. This cartilage, described in the literature as triangular fibrocartilage, articular disc, or meniscus at the wrist, as its name suggests, has a triangular shape. Its broad base is attached to the distal margin of the ulnar notch of the radius, and its apex to the base of the ulnar styloid. It looks like a cover adapting itself to the head of the ulna, separating it from the parallel carpal bones—the lunate and triquetrous bones. The borders of the fibrocartilage are thick in comparison with its center which is less than 1 millimeter in thickness. On its carpal surface there is a strong ligament blended

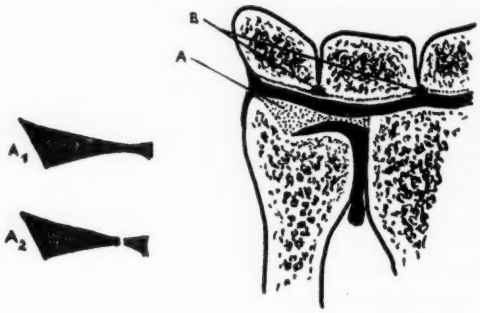


FIG. 1. The drawing shows the correlation between the wrist joint and the other adjacent joints. The interosseus intercarpal ligament, *B*, prevents the communication to the small joints in the proximal carpal row; the triangular fibrocartilage, *A*, prevents the communication to the radioulnar joint. In a frontal section the fibrocartilage appears as two triangles which unite in its radial third, A_1. When the continuity of the fibrocartilage is disturbed, the triangles remain separated, A_2.

inseparably to it. The dimension of the disc varies according to the space between the bones to which it is inserted. In a frontal section the fibrocartilage appears as two triangles which unite in its radial third, the bigger one being attached to the base of the ulnar styloid process and the smaller one to the border of the ulnar notch of the radius. In case the continuity is disturbed, the triangles remain separated (Fig. 1).

Our investigation was also directed to the adjacent radioulnar articulation which is often involved in injuries of the wrist joint. It is formed by the articular surfaces of the radius, ulna, and triangular disc. The joint capsule is extremely lax (to permit rotation) and upward forms a recess—recessus sacciformis—between the radius and ulna.

The theoretic assumption for our study was that there is a possibility of damage to the joint ligaments, to the bone cartilage, or to the discus. This damage cannot be determined by regular roentgenographic examination, and only the introduction of a contrast medium renders this determination possible. We expected to see in these cases penetration of the medium into irregular places as a sign of rupture in the internal ligament apparatus.

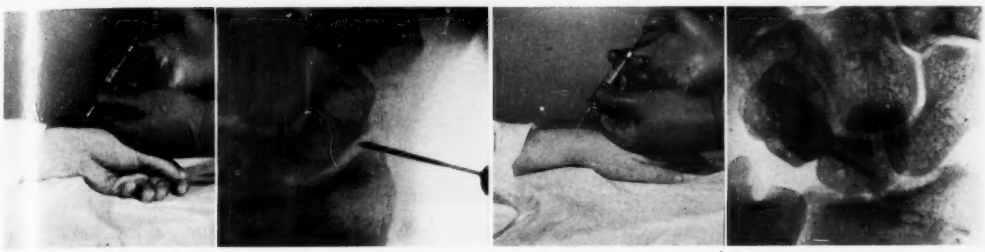
TABLE I.—WRIST JOINT ARTHROGRAMS ON SPECIMEN MATERIAL

Group	*No. of males*	*No. of females*	*Total*
Penetration into the radioulnar joint	3	1	4
Penetration into the intercarpal joint	6	3	9
No penetration	34	13	47
Totals	43	17	60

METHOD

Anatomic material. Sixty wrist joints in anatomic specimens were studied in this phase of the investigation. This material was examined in the Department of Pathology, Belinson Hospital, and in the Institute of Forensic Medicine, Tel-Aviv. Wrist joints were studied in specimens from individuals ranging in age from 14 to 76 years, without previous predilection; 17 of them in females and 43 in males. The examinations were performed 5 to 48 hours after death. Seven of the wrists were examined in bodies in which death was due to trauma, and in the remainder death resulted from other causes.

In these examinations we used the regular diodone B.P. 35 per cent solutions. The contrast medium was injected either between the styloid process of the radius and the scaphoid bone in the middle of the anatomic snuffbox or between the distal border of the radius and the bones of the proximal carpal row (Fig. 2a and b). By the second path, the space is wider and therefore such great precision is not required as is the first one, in which a slight alteration of the needle position may bring the contrast solution into the adjacent carpal joints. After puncture, 2 to 3 cubic centimeters of neutral solution —water or physiologic saline—were injected. In case the injection was intra-articular, the fluid filled the joint and returned back through the needle in a gush; if the injection was extra-articular the site of the puncture swelled and the fluid did not flow back. This sign was used as an indicator to continue or to stop the procedure. Once intra-articular location was assured, the same amount of contrast solution was introduced into the joint cavity. Anteroposterior and oblique views were taken.



a b

FIG. 2. Two methods for wrist joint puncture. The needle is inserted, a, between the radial styloid process and the scaphoid bone or, b, between the distal border of the radius and the bones of the proximal carpal row.

The normal arthrogram corresponds with the anatomic details of the joint. The contrast solution fills the joint which appears in the picture as a continuous even line. In all cases, we have seen in the neighborhood of the ulnar styloid, at the medial end of the contrast line, a pea sized filling of a recess or bursa connected with the joint cavity (Fig. 3). This is assumed to be a regular anatomic detail which is adapted to the radiocarpal joint.

This typical picture was found in 47 wrist joint arthrograms (Table I). In 9 arthrograms, the contrast solution penetrated the intercarpal joint and appeared as small branches originating from the basal line and spreading between the scaphoid and lunatum, and between the lunatum and triquetrum. From these points the solution scatters between all the small bones of the intercarpal joint (Fig. 4). In 4 arthrograms the solution penetrated through the articular disc into the distal radioulnar joint. In these cases a further contrast line was seen between the articular disc and the head of the ulna so that the arthrographic picture appeared like a frontal section of the disc: 2 triangles separated in the radial third. These 4 arthrograms showing penetration into the radioulnar joint were carried out on specimens, 2 of which were from a male and a female 60 years old, the third from a 42 year old patient (specimen 27), and the fourth from a 29 year old patient (specimen 22).

SPECIMEN 27. The two wrist joints of a 42 year old male were examined. The cause of death was suicide through hanging. Arthrography of the right wrist joint showed penetration of contrast solution into the distal radioulnar joint. A normal arthrogram was obtained from the left wrist. In dissection, a round defect of the right articular disc was discovered, which explained the finding in the arthrogram. In the left wrist the disc was normal (Fig. 5). The histologic examination showed degenerative changes of both articular discs, more extensive around the perforation of the right disc.

SPECIMEN 22. An upper left limb, belonging to a 29 year old male and amputated traumatically at the shoulder, was examined. In the wrist region subcutaneous hematomas and superficial scratches were observed, without fractures of the bones in the neighborhood. Arthrography of the wrist joint showed penetration of the contrast solution through the articular disc into the distal radioulnar joint. In dissection, scattered hemorrhages were found in the soft tissues. The joint itself did not appear to be damaged. In the articular disc a 3 millimeter long fissure was observed near the attachment of the disc to the lower end of the radius (Fig. 6). Histologic examination revealed early degenerative changes of the cartilage in the perifissural area.

In the 2 specimens from individuals more than 60 years old, round defects and advanced degenerative changes of the cartilage were observed.

Clinical material. Contrast arthrograms were performed in 24 males with wrist injuries. The patients were chosen at random with various indeterminate complaints which followed wrist injuries with or without lesions of the bones. Their ages varied from 26 to 57 years. The same method was used as in the specimens: 35 per cent diodone was in-

FIG. 3. The normal arthrogram in three different wrists shows a continuous line with a full recessus in the ulnar side.

jected after the introduction (as a test) of 1 per cent novocain. In most cases, the solution was injected between the distal border of the radius and the bones of the proximal carpal row because of the advantage of this site as previously explained. After completing the examination, the wrist was immobilized in a plaster cast for 2 days to prevent synovial reactions. This step was taken as a precaution in accordance with our experience with the same contrast solution used in arthrograms of the knee. The roentgenograms were taken in four views: anteroposterior, posteroanterior, oblique, and lateral. The general rules of arthrographic technique were observed—maximum sterility and strict intra-articular introduction of the solution. In the reported series there have been no complications resulting from the procedure.

In accordance with the results of the arthrograms, the clinical material can be divided as follows: in 11 instances, penetration of the contrast solution through the articular disc into the distal radioulnar joint was observed, in 7 cases, fractures of the lower end of the radius preceded, in 4 cases no bone lesions preceded examination.

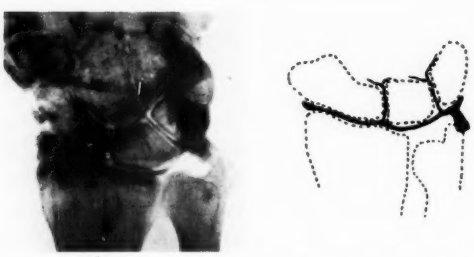


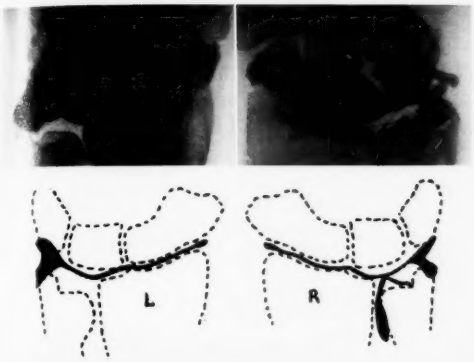
FIG. 4. The roentgenogram reveals penetration of the contrast medium into the intercarpal joint.

CASE 1. A 45 year old police officer was examined in our department 16 months after injury. He had suffered from pains in his right wrist after trying to hold another person by force which resulted in strong torsion of the wrist. When 3 months passed without improvement, he went for examination and treatment to one of the local clinics. When several injections of hydrocortone and immobilization of the wrist in a plaster cast for 2 months failed to relieve his condition, he was sent to us for further investigation. Clinically, painful rotational movements of the wrist, especially supination, and tenderness about the ulnar site were observed. No swelling was found, and a simple roentgenogram did not reveal any changes. Arthrography showed penetration of the contrast solution into the distal radioulnar joint (Fig. 7).

CASE 2. A 30 year old man was sent to our department with a diagnosis of Colles' fracture after a fall during work. He had been treated in one of the local hospitals by reduction and plaster cast immobilization. The roentgenographic examination showed a fracture of the distal radial end with good position of the fragments. Six weeks later the plaster cast was removed and the patient was sent for physical treatment. Fourteen weeks after the injury, the examination revealed swelling of the wrist joint, tenderness upon pressure, and limitation of movements, particularly supination. In this case, arthrography of the wrist joint was performed. The roentgenogram showed penetration of the contrast medium into the distal radioulnar joint and an accumulation of the medium at the intra-articular fracture line (Fig. 8).

In 9 cases, no changes were observed in the arthrogram. In 3 of these cases, the examination followed fractures of the lower end of the radius; in 5 no fractures preceded examination; and in 1 case Colles' fracture combined with fracture dislocation of the ulnar styloid preceded the examination.

CASE 3. A 49 year old building worker was sent to us immediately after injury. The roentgenogram showed a comminuted intra-articular fracture of the distal end of the radius with dorsal displacement, and



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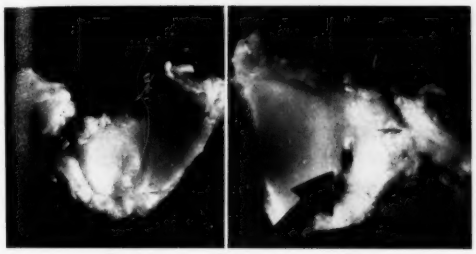

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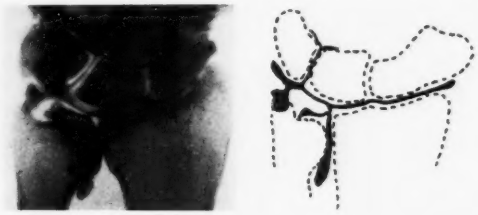
FIG. 5.



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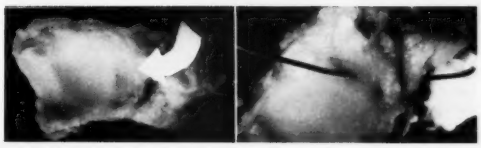


b

FIG. 6.

FIG. 5. Specimen 27. a, The roentgenogram of the right wrist shows penetration of the contrast solution into the distal radioulnar joint; b, the anatomic specimen with perforation of the disc. The arthrogram shows a normal left wrist joint; the articular disc was complete.

FIG. 6. Specimen 22. a, The arthrogram shows penetration of the contrast material into the distal radioulnar joint. b, In the articular disc a 3 millimeter long fissure is seen.

an additional fracture of the ulnar styloid with radial dislocation. Reduction and immobilization in a plaster cast were performed. Because of slow improvement of the clinical condition, an arthrographic examination was performed 3 months after the injury. In spite of the displacement and the shortening of the lower end of the radius, no penetration of the contrast medium through the articular disc was observed (Fig. 9).

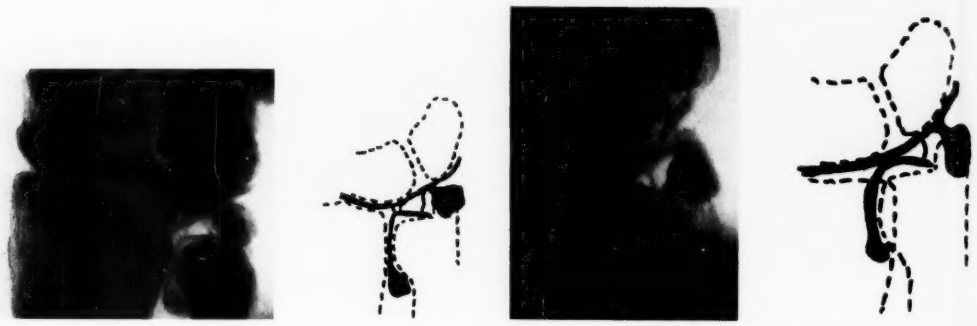
In 4 cases, penetration of the contrast solution into the intercarpal joint was found. In 1 of these, there was a fracture of the distal radial end, and in the others, there were no lesions of the bones (Table II). In 1 case the solution penetrated into the joint between the triquetrum and pisiform bones.

COMMENT

It is premature yet to draw conclusions on the value of wrist joint arthrography as a method for elucidating indeterminate conditions in this area. Our intention was to present herein positive impressions of the primary results of this technique in the knowledge that while a foolproof diagnostic technique for detecting obscure disorders in the wrist area had not yet been attained, possibly filling the radiocarpal joint with contrast material would prove to be an effective measure.

Ulnar styloid bursa. An interesting fact in our first trials was the filling of a bursa or recessus on the ulnar side of the wrist joint. The position of this finding corresponds almost to the places of calcification described in some articles as "calcification about the flexor carpi ulnaris tendon." It appears to us that one should differentiate between these cases and those of calcification above the pisiform bone, and that one should not attribute both to the same calcification process around the flexor carpi ulnaris tendon. In our opinion, many pathologic states of pain, swelling of the wrist, and calcification could be related to a process in the area of the aforementioned bursa.

Köhler presented a roentgenogram showing calcification in the ulnar end of the wrist



a b

FIG. 7. Case 1. a, In the anteroposterior position, the roentgenogram shows penetration of the contrast medium through the articular disc, in 3 places, into the distal radioulnar joint. b, In the oblique position, only 1 line of penetration is seen.

joint and interpretated this finding as calcification of the articular disc. The site of this finding also corresponds exactly to the ulnar styloid bursa and it should be included in the calcification group.

Research in this line would bring interesting data for diagnostic and therapeutic methods.

Triangular fibrocartilage. Various conditions are incorporated under the noncommittal term of wrist disability. One of these conditions, possibly the most frequent, is the occasional disability of the wrist joint after fractures at the typical site of the radius. The fracture line in these cases often penetrates into the lower part of the radioulnar joint and causes its loss of integrity. In cases of marked displacement in radius fractures, the damage of the radioulnar joint is limited by the articular disc which is treated according to the grade of displacement. This tension can be the cause for tears of the articular disc. According to Gartland and Werley, avulsion of the distal end of the radius, which contains the ulnar notch, or avulsion of the base of the ulnar styloid occasionally prevents rupture of the disc. Actually, there are three possibilities in traumatic conditions around the articular disc: The first consists of fractures of the radius with displacement, including avulsion of the bone at the insertion of the disc. In these cases, the disc remains intact (Case 3, Fig. 9). A second possibility is similar fractures of the radius in which the mechanism of injury does not cause avulsions at the insertions of the disc. In this second group, the tension affects the cartilage and causes its rupture (Case 2, Fig. 8). There is also a third possibility of wrist injury concentrated in the region of the articular disc that does not cause any bone changes but only tears of the cartilage (Case 1, Fig. 7). In this last group there is the clinical picture of wrist derangement without roentgenographic findings, whereas the location of the damage can only be suspected.

TABLE II.—WRIST JOINT ARTHROGRAMS ON CLINICAL MATERIAL

Group	*No. with fractures*	*No. without fractures*	*Total*
Penetration into the radioulnar joint	7	4	11
Penetration into the intercarpal joint	1	3	4
No penetration	4	5	9

Filling of the wrist joint with contrast medium indicates damage of the disc when penetration of the medium through the disc into the lower radioulnar joint is observed.

In the literature, the incidence of perforation of the articular disc, has been described variously. According to Johnston, the disc is usually complete. Some have found the perforation only occasionally. According to Testut this condition is noted frequently. According to our findings, arthrography of 60 specimens demonstrated penetration of the contrast medium

through the disc in only 4 cases. In the clinical group, the ratio of penetration was larger—11 penetrations into the lower end of the radioulnar joint in 24 wrist joint arthrograms (45.8 per cent). The penetration of contrast medium through the articular disc indicates discontinuity of the disc. The frequency of penetration in clinical cases as compared with specimens indicates the traumatic reasons for articular disc discontinuity.

As already mentioned, some investigators assume that the triangular fibrocartilage is normally complete. Frazer and Robbins pointed out that the radiocarpal and lower radioulnar joints are essentially distinct, and when they communicate this is a secondary communication, pathologic in its causation.

In 1956, establishing tears of the triangular fibrocartilage, Coleman presented 4 cases in which tears were demonstrated at operation. He also described the mechanism of injury as hyperextension rotational strain of the wrist.

Grant described articular disc perforation as an anteroposterior fissure at the beginning which in time becomes a round hole. It is not difficult to understand the reason for the fissure becoming round. Regarding the origin of the fissure, arthrographic data also prove its traumatic cause, in some cases possibly on the basis of previous degeneration of the cartilage. Of significant importance in this direction are also specimens 22 and 27. In the former, a fresh tear appeared as a fissure and histologic examination revealed early degenerative changes in the cartilage; in the latter, the form of the tear was round (showing persistence) and the histologic examination revealed advanced degenerative changes.

Penetration of the contrast medium through the articular disc into the lower end of the radioulnar joint in arthrograms of the wrist joint gives some indication of the condition of the disc and adds to the understanding of different complaints in uncertain cases. Positive findings in arthrograms of the wrist joint do not prove that

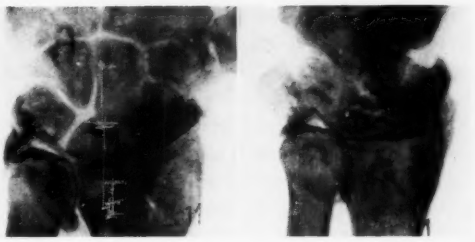


FIG. 8. Case 2. Tear of the triangular fibrocartilage. In the anteroposterior and oblique positions, the roentgenograms show penetration of the contrast medium into the radioulnar joint.

the disc lesion results from the present trauma just as positive findings in arthrograms of the knee reveal lesions of the meniscus but do not prove the time relationship. The solution of this question and the problem of treatment are based on the clinical state only.

Communication with the intercarpal joint. In spite of the description by Johnston and others of the intercarpal joint as a separated one, and the allegation of Testut that communication between this joint and the radiocarpal joint is possible only in rare cases, our findings after arthrography show something different. In our clinical material penetration of the contrast medium from the wrist joint into the intercarpal joint was noted in 4 cases. In arthrograms of specimens, the medium penetrated in 9 cases. In the present stage of our investigation, no final statement is possible. It appears that arthrography may add, more precisely, many details which the simple anatomic techniques do not reveal. We are not under the impression that trauma can be the cause of penetration of the contrast medium into the intercarpal joint; furthermore, study of the

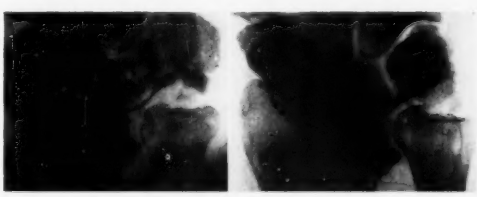


FIG. 9. Case 3. In spite of the shortening and deformity of the lower radial end, no penetration of the contrast medium into the radioulnar joint was observed.

clinical material and the specimens does not lead in this direction.

Other findings. One of the characteristics of a contrast solution is to penetrate and fill every space. In cases of lesions of the articular surfaces of bones which cannot be diagnosed by simple roentgenographic examination, accumulation of the contrast medium will reveal it. In such cases, thickening of the contrast line in the respective place of a particular bone indicates damage of its articular surface (Fig. 8). On the basis mentioned, this will enable early diagnosis of posttraumatic intra-articular changes before it can be detected in simple roentgenograms.

SUMMARY

Techniques of wrist joint arthrography with contrast medium have been described. Arthrography was performed in 24 cases of various injuries in the wrist joint area. Arthrograms were also made of 60 wrists from anatomic specimens, comparing results.

A bursa or recessus at the ulnar end of the wrist joint that filled with contrast medium was described. Its clinical value was discussed from the theoretic point of view.

A basis for the possibility of detecting pathologic processes invisible in simple roentgenograms, especially tears of the triangular fibrocartilage at the wrist, was discussed.

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LYMPHATIC STUDIES PERTAINING TO LOCAL SPREAD OF CARCINOMA OF THE RECTUM IN THE FEMALE

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THE PROXIMITY of the female internal genitalia to the rectum presents a problem during resection of the rectum for carcinoma: whether the internal genitalia, entirely or partly, should be removed with the rectum in order to reduce the high incidence of local recurrence.

The high incidence of local recurrence that follows excision of the rectum for carcinoma below the peritoneal reflection has been noted by many investigators. A number of reports have emphasized the high rate of local recurrence involving the female internal genitalia. Reinhold reported a series of 35 cases in which carcinoma of the rectum involved the rectovaginal septum. He found that invasion of the perirectal tissues and the rectovaginal septum may take place before invasion of the superior hemorrhoidal and hypogastric lymph nodes. Chlyvitch, in studying 581 cases of cancer of the rectum in the female, found involvement of the posterior wall of the vagina in 24 per cent, of the uterus in 6 per cent, and of the ovaries in 2 per cent. As for postoperative recurrences, he found that 70 per cent were local and, of these, that 72 per cent were found in the rectovaginal septum. He believed that the anterior wall of the rectum, the rectovaginal septum, and the posterior wall of the vagina form an indivisible entity, from anatomic, pathologic, clinical, and therapeutic points of view, with regard to cancer in this region. For cancer of the lower part of the rectum in the female, especially on the anterior wall, he concluded that the procedure of choice should be abdominoperineal resection of the rectum, combined with hysterectomy and resection of the posterior wall of the vagina. Schwartz, for low-lying carcinoma of the rectum, advocated the use of abdominoperineal resection of the rectum combined with hysterectomy and resection of the posterior vaginal wall. He was the first to perform this procedure as an "operation of election," in contradistinction to an "operation of necessity," when the cancer has already invaded portions of the internal genitalia. Deddish found residual disease common in the female genital tract, especially in the posterior vagina, the ovaries, and the uterus after standard abdominoperineal resections. "It was quite apparent," he wrote, "that a more extensive effort must be made to remove the primary rectal cancer and its regional lymphatic drainage areas." Stearns and Deddish mention finding metastasis to the ovaries in 18 per cent of Duke's class C rectal cancers. Sedgwick and Wainstein found invasion of the vagina in 4 of 28 cases of epidermoid carcinoma of the anus. Buxton found invasion of the posterior vaginal wall so common with epidermoid carcinoma of the anus, that he advised removal of the posterior vaginal wall in resections for epidermoid carcinoma of the anus.

Lymphatic pathways from the rectum to the female internal genitalia have been described by Morau and Villemin and associates. None of these studies has been a complete investigation of the problem. The present study was carried out in order to delineate more clearly the lymphatic pathways from the anus and rectum, at different

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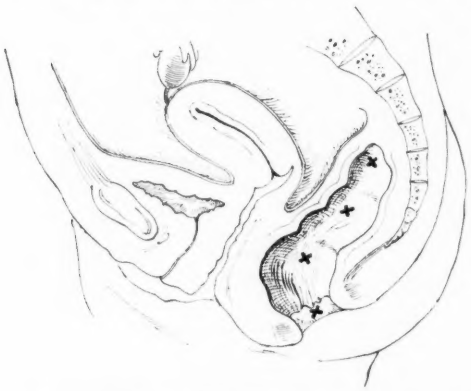


FIG. 1. Diagram illustrating sites of experimental injections of direct sky blue dye.

levels, to the female genitalia as a possible explanation of this high incidence of local recurrence.

METHOD OF STUDY

The vital dye, direct sky blue, was selected for this study because it has been used satisfactorily for clinical studies of lymphatic pathways by many investigators. Subjects for study were female patients about to undergo operation for gynecologic or rectal conditions. Seventy-five patients subjected to hysterectomy and 15 patients undergoing abdominoperineal resection of the rectum for cancer were studied. One to two cubic centimeters of dye in 4 per cent dilution were injected into the anus and rectum at the following sites (Fig. 1) 12 to 18 hours before operation: (1) subcutaneously, in the anal canal, in all quadrants; (2) submucosally, in the rectum, 2 inches above the anal verge, in all quadrants; (3) submucosally, in the rectum, 4 inches above the anal verge, in all quadrants; and (4) submucosally, in the rectum, or rectosigmoid region, 6 inches above the anal verge, in all quadrants.

During the operation, note was made of the spread of dye. Because complete dissections could not be made in every case, information from many observations were pieced together. The following areas were specifically examined for the spread of dye: the mesorectum, mesosigmoid, and preaortic tissues; the lateral stalks and hypogastric tissues; the levatores ani and ischiorectal tissues; the cul-de-sac, uterosacral ligaments, broad ligaments, anterior vaginal wall, posterior vaginal wall, cervix, body of the uterus, Fallopian tubes, and the ovaries; the ureters and periureteral tissues; and the pericystic tissues.

A time interval of approximately 12 hours between the time of injection and that of the operation was chosen because a longer period of time would have allowed the dye to spread to more distant structures. This further spread would have nullified the purpose of the study which was to determine the most direct lymphatic routes from the rectum to the genitalia. The injection of large amounts of dye tended to vitiate results, because the dye spread into the accessory lymphatics throughout the pelvis and was absorbed into the blood stream, resulting in generalized tissue staining. One to two cubic centimeters of dye, depending upon the size of the patient, gave optimum results.

RESULTS

When the dye is injected into the anal canal (Fig. 2), it reveals considerable spread upward through the mesorectum, mesosigmoid and para-aortic areas. A good deal of dye enters the perirectal space, stains the rectovaginal septum and lower two thirds of the posterior vaginal wall, and then passes upward through the mesorectum and mesosigmoid. When the injection is made into the anterior quadrant of the anal circumference, more dye passes into the rectovaginal septum and posterior wall of the vagina than when the posterior quadrant is so injected. There is no spread to the broad ligaments, cul-de-sac, uterus, ovaries, and tubes. Lateral and downward spread is considerable, strongly staining the lateral stalks, hypogastric nodes, levatores ani, and ischiorectal tissues. Considerable dye is carried to the inguinal lymph nodes, thence to the iliac and aortic nodes. If the injection

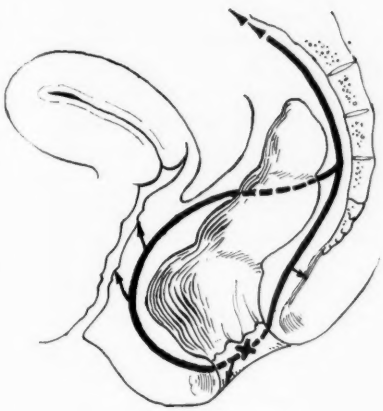


FIG. 2.

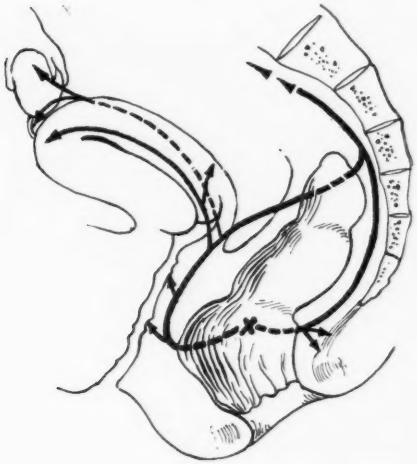


FIG. 3.

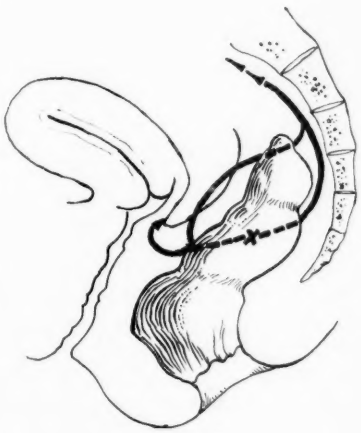


FIG. 4.

FIG. 5.

FIG. 2. Diagram illustrating spread of dye when injection is made subcutaneously in anal canal.
FIG. 3. Diagram illustrating spread of dye when injection is made submucosally 2 inches above the anal verge.
FIG. 4. Diagram illustrating the spread of dye when the injection is made submucosally 4 inches above the anal verge.
FIG. 5. Diagram illustrating spread of dye when injection is made 6 inches above the anal verge.

is made on the lateral aspect of the anus, the dye is carried mainly to the ipsilateral inguinal nodes.

Dye injected 2 inches above the anal verge (Fig. 3) exhibits a most extensive lymphatic distribution. In a downward direction, the pelvic diaphragm is strongly stained throughout its extent, and the ischiorectal tissues are less strongly stained. This downward lymphatic distribution has been previously described by Block. There is intensive spread of dye into the perirectal space, the rectovaginal septum, the posterior vaginal wall, the cul-de-sac, and broad ligaments and much less spread in the uterus, salpinges, and ovaries. There is heavy spread

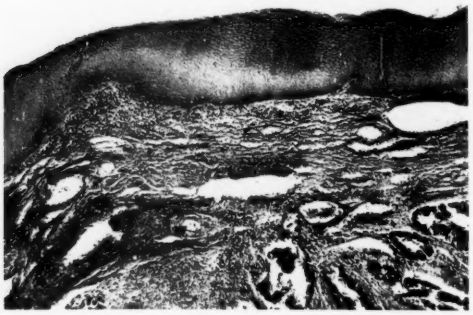


FIG. 6. Low-power photomicrograph of the rectovaginal septum in a patient with adenocarcinoma situated on the anterior aspect of the lower part of the rectum. There was no gross invasion. Note proximity of the posterior vaginal wall to the tumor.

of dye into the lateral pelvic and hypogastric nodes. Upward spread is intensive through the mesorectal, mesosigmoid, and aortic nodes. Although French surgeons emphasize the increased risk with lesions on the anterior aspect of the lower rectum, "le face dangereux," injections into the lateral and posterior aspects have the same dye distribution. With a longer period of observation, 24 hours for instance, the dye spreads around to the anterior vaginal wall and the tissues at the base of the bladder.

TABLE I.—SUMMARY OF RESULTS

		Anal level	*2 inches above verge*	*4 inches above verge*	*6 inches above verge*
Mesorectum		++++	++++	++++	++++
Mesosigmoid		++++	++++	++++	++++
Para-aortic nodes		+++	+++	+++	+++
Lateral stalks		++	++++	++	0
Hypogastric nodes		++	++++	++	0
Vagina	anterior	0	0 to ++	0	0
	posterior	+++	++++	0	0
	(lower ⅔)		++++	0	0
Uterus	corpus	0	++	0	0
	cervix	0	++	0	0
Broad ligaments		0	++++	+++	0
Cul-de-sac		0	++++	++++	0
Tubes		0	++	0	0
Ovaries		0	++	0	0
Ureteral, periureteral		0	0	0	0
Perivesical		0	0 to ++	0	0
Levator ani		++++	++++	0	0
Ischiorectal fossae		++++	+++	0	0
Inguinal nodes		++++	0	0	0

0 No staining by dye; + slight staining by dye; ++ moderate staining; +++ heavy staining; ++++ very heavy staining.

It was noted that the spread of dye into the uterus and ovaries was definitely decreased in females who had passed the menopause. Postmenopausal atrophy of the lymphatics may be the most likely explanation. It was also noted that the ureter and periureteral tissues were not stained by the dye but that they passed unscathed through the deeply stained broad ligament and hypogastric tissues.

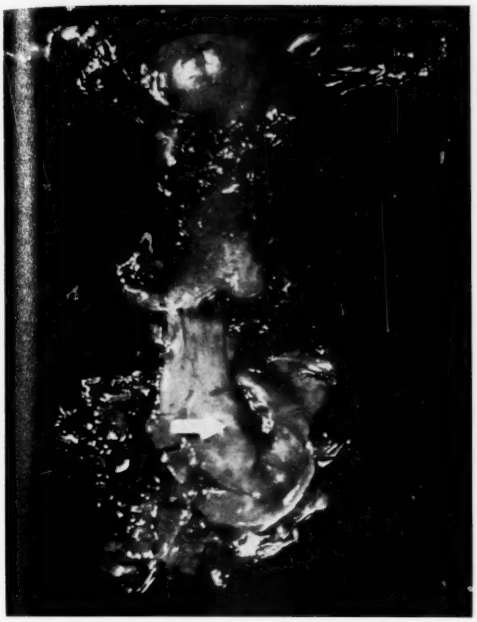
Injection of dye 4 inches above the anal verge (Fig. 4) shows circumferential spread at the level of the injection, spread into the cul-de-sac, the posterior lower portion of the broad ligaments, the uterosacral ligaments, and often the upper one fourth of the posterior vaginal wall. There is some spread to the hypogastric nodes, thence to the aortic nodes. Most spread is upward through the mesorectum and mesosigmoid nodes, thence to the aortic nodes. There is no spread into the anterior or lower posterior vaginal walls, uterus, tubes, or ovaries and no spread was noted in a downward direction into the levatores ani or ischiorectal tissues.

Injection of dye 6 inches above the anal verge (Fig. 5) causes a 2 to 3 centimeter band of circumferential spread at the level of injection. From there, the spread is all upward, through the mesosigmoid and aortic nodes. There is no staining of the female genitalia or cul-de-sac.

It was noted that lymphatic vessels form within adhesions, corroborating the findings of Simer and Webb and others. If omentum were adherent to an organ which was stained with dye, the dye would pass into the lymphatics of the omentum. In one case, in which a loop of ileum was adherent to the corpus uteri, the dye passed from the uterus through the adhesions into the serosa of the ileum, thence into the nodes in the mesentery of the ileac loop.

DISCUSSION AND CONCLUSIONS

The problem of local recurrence after removal of the rectum for carcinoma is serious. It seems strange that the trend of recent surgical attack has been to increase



a

b

FIG. 7. a, Photograph of operative specimen consisting of uterus and adnexa and vagina. The patient had an abdominoperineal resection of the rectum performed 5 years before for low-lying carcinoma of the rectum. The arrow points to recurring adenocarcinoma in the posterior vaginal wall. b, Photomicrograph, taken from specimen in "a," demonstrates adenocarcinoma of the rectum recurring in the posterior wall of the vagina.

the scope of excision for the distant lymphatic spread and to neglect local lymphatic spread. One finds that the usual operative procedure embraces a wide area proximal to the lesion but a very narrow area at the site of the lesion itself. Often the rectum must be "shaved off" the neighboring organs.

The lymphatic studies described here indicate the close connections between the rectum and the female genitalia. These studies corroborate clinical observations regarding the location of metastatic and recurrent lesions (Figs. 6 and 7). Anatomic studies indicate that there is no real septum between the rectum and vagina and that the perirectal, perivaginal, rectovaginal, and broad ligament tissues are all continuous.

From the lymphatic map, delineated by the dye studies, one may conclude that a more radical approach should be adopted for cancer of the rectum in the female:

1. For epidermoid carcinoma of the anus, an abdominoperineal resection of the rectum, with aortic, iliac, and pelvic node dissection, a wide perineal excision, and excision of the lower two thirds of the posterior vaginal wall should be carried out. An inguinal node dissection should be performed routinely, probably at a later date.

2. For carcinoma 2 inches above the anal verge, abdominoperineal resection of the rectum should be performed, with aortic and pelvic node dissection and with resection of the uterus, ovaries, tubes, broad ligaments, cul-de-sac, and entire posterior wall of the vagina, all in continuity.

3. For carcinoma 4 inches above the anal verge, abdominoperineal resection of the rectum, with aortic and pelvic node dissection and resection of the uterus, ovaries, tubes, broad ligaments, cul-de-sac, and upper one third of the posterior vaginal

wall should be carried out, all in continuity. A sphincter-saving operation may be considered since there is apparently no spread of dye into the levator ani, sphincter, or ischiorectal tissues.

4. For carcinoma 6 inches above the anal verge, anterior resection is apparently adequate therapy.

The dye experiments reveal lymphatic pathways from the lower part of the rectum to the ovaries but none from the upper part of the rectum or colon. Ovarian cancer secondary to cancer of the colon has an extremely poor prognosis since the mechanisms of spread are via retrograde lymphatics, transperitoneal seeding, or the blood stream. Therefore, the addition of simple, discontinuous oophorectomy to a resection of the rectum for cancer arising at any level does not seem logical; it is inadequate for lesions of the lower part of the rectum and ineffectual for lesions of the upper part of the rectum and colon.

SUMMARY AND CONCLUSIONS

1. Lymphatic pathways from the anus and rectum to the female genitalia were mapped out by means of vital dye studies in order to clarify the high incidence of residual carcinoma in the female genitalia after resection for carcinoma of the rectum and anus.

2. For carcinoma of the anal canal, the lymphatic map indicates that excision of the lower two thirds of the posterior vaginal wall should be added to abdominoperineal resection of the rectum.

3. For carcinoma of the lower part of the rectum, hysterectomy, oophorectomy, and excision of the broad ligaments and posterior vaginal wall should be added, in continuity, to abdominoperineal resection of the rectum.

4. For carcinoma of the midrectum, the same procedure is indicated, except that only the upper one third of the posterior part of the vaginal wall would need to be removed.

5. For carcinoma of the upper part of the rectum and rectosigmoid, the lymphatic map indicates that anterior resection is an adequate operation.

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AN EVALUATION OF THE DEVELOPMENT OF PORTOSYSTEMIC COLLATERALS IN ASCITES

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THE EXACT NATURE of the portal collateralization in ascites has not been completely determined. In dogs with supradiaphragmatic constriction of the inferior vena cava, a collateral system develops which bypasses the obstruction. Previous studies have shown that inferior vena caval-systemic collaterals are the major avenue for the return of blood to the heart. The importance of portosystemic collaterals has been questioned by Stewart and his associates. It was, therefore, our purpose to carry out the following study in an effort to demonstrate not only the presence of portosystemic collaterals but also to determine their functional capacity in the dog with experimental ascites.

METHOD

Two series of experiments were performed in both normal control dogs and dogs in which supradiaphragmatic constriction of the inferior vena cava had been performed 1 to 8½ months previously. Adult male and female mongrel dogs weighing 12 to 18 kilograms were anesthetized with intravenous thiopental (20 milligrams per kilogram).

In the first series, 4 dogs, 5½ to 8 months after caval constriction and 4 control dogs were used. The abdomen was entered through a midline incision. After the porta hepatis was exposed, a heavy silk ligature was placed loosely about the portal vein cephalad to the entrance of the gastroduodenal vein. The ends of the silk ligature were attached to a Rumel tourniquet in order to occlude the portal vein during the subsequent procedure. A polyethylene catheter was inserted into one of the splenic veins. Another catheter was passed into the femoral artery and connected to a Statham strain gauge. Arterial pressure was monitored on a Sanborn 550 M recorder. A three-way stopcock was interposed in the femoral arterial tubing in order to periodically collect blood samples. After obtaining a baseline blood sample, a continuous recording of arterial pressure was begun. The portal vein was then completely occluded with the Rumel tourniquet and Evans blue dye (50 milligrams per 15 kilograms) immediately injected into the splenic vein catheter. This was washed into the portal system with 2 milliliters of saline. At 1 minute intervals, 5 milliliter samples of blood were collected from the femoral artery into heparinized tubes. Following the fifth sample, the portal vein was released and 4 additional blood samples were collected. Determination of Evans blue dye concentration was performed in the following manner: with the baseline plasma for a blank, the optical densities of the samples were read on a Coleman Jr. spectrophotometer at 625 millimicrons.

In the second series, 12 dogs in which supradiaphragmatic constriction of the inferior vena cava had been performed 3 weeks to 8½ months previously and 5 control dogs were used. The animals were intubated and the endotracheal tube was connected to an automatic respirator. The abdomen was entered through a midline incision, and the ascitic fluid removed and

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TABLE I.—THE CORRELATION OF CHANGES IN SYSTEMIC PRESSURE WITH THE APPEARANCE OF EVANS BLUE DYE IN THE SYSTEMIC CIRCULATION UPON OCCLUSION AND SUBSEQUENT RELEASE OF THE PORTAL VEIN

	Normal dogs								*I.V.C. constricted dogs*							
	1503		*447*		*1112*		*1781*		*1030*		*1315*		*1051*		*1263*	
	B.p. mm. Hg	*Opt. dens.*	*B.p. mm. Hg*	*Opt. dens.*	*B.p. mm. Hg*	*Opt. dens.*	*B.p. mm. Hg*	*Opt. dens.*	*B.p. mm. Hg*	*Opt. dens.*	*B.p. mm. Hg*	*Opt. dens.*	*B.p. mm. Hg*	*Opt. dens.*	*B.p. mm. Hg*	*Opt. dens.*
Baseline	140	0	125	0	140	0	120	0	90	0	160	0	80	0	130	0
Occlude PV																
1 minute	100	.030	120	.020	100	.020	110	.079	75	.270	140	.400	60	.270	125	.300
2 minutes	90	.020	100	.020	100	.020	100	.109	65	.270	130	.350	60	.220	125	.230
3 minutes	85	.020	90	.020	95	.050	100	.109	60	.240	130	.360	60	.210	120	.230
4 minutes	80	.020	90	.010	90	.050	90	.098	70	.210	130	.340	70	.190	115	.230
5 minutes	80	.015	90	.020	80	.060	80	.109	60	.195	130	.330	60	.190	115	.220
Release PV																
6 minutes	90	.280	115	.240	105	.310	110	.450	70	.180	145	.350	65	.185	125	.210
7 minutes	100	.370	120	.310	130	.350	120	.322	75	.210	155	.330	65	.180	125	.200
8 minutes	135	.470	120	.300	135	.330	110	.300	80	.240	150	.320	65	.170	130	.190
9 minutes	135	.400	120	.290	135	.320	110	.290	75	.240	150	.310	70	.175	130	.180

Opt. dens., optical density of arterial plasma.
PV, Portal vein.

measured. After exposing the porta hepatis, the portal vein was isolated between the hilus of the liver and its last tributary, the gastroduodenal vein. This segment of portal vein was doubly ligated and divided. After observing the appearance of the bowel and its mesentery for approximately 5 minutes, the abdomen was closed. Assisted respiration was maintained postoperatively until spontaneous breathing could be initiated. The animals received intravenous infusion of 5 per cent glucose in water during the procedure in amounts varying from 200 to 500 milliliters. In all dogs that survived portal vein division, portal angiograms were obtained on the second postoperative day. These were accomplished by injecting 20 to 30 milliliters of 70 per cent urokon into a mesenteric vein. Postmortem examination, with particular attention to the portal vasculature, was performed in all animals.

RESULTS

Injection of Evans blue dye into the portal bed of normal dogs during occlusion of the portal vein at the porta hepatis gave a uniform pattern for the appearance of dye in the systemic circuit (Fig. 1a). During occlusion of the portal vein, small amounts of dye appeared in the arterial blood samples. In 2 samples there was a small but definite tendency for the concentration of dye to rise during the period of occlusion. Upon release of the portal vein, there was an immediate increase in the concentration of dye to comparatively high levels in all normal animals. Thereafter, dye concentration tended to rise during the first 2 minutes after release of the portal vein, then decline in a linear fashion.

In constricted dogs, there was also a characteristic pattern for the appearance of dye in the general circulation (Fig. 1b). The highest dye concentration appeared in the first minute sample during occlusion of the portal vein. The dye concentration, thereafter, declined at varying rates during the period of portal occlusion. Upon release of the portal vein in 2 animals, the dye concentration continued to diminish at essentially the same rate. In 2 animals there was a slight to moderate rise in dye concentration in the postocclusive period. In 1 animal that was constricted only 1 month prior to this study, an intermediate pattern for the appearance of the dye was noted.

Arterial blood pressure fell in both groups of animals during the period of portal vein

occlusion (Table I). There was a greater mean fall (50 millimeters of mercury) in the normal group than in the chronically constricted dogs (25 millimeters of mercury).

Acute ligation and division of the portal vein (Table II) was performed on 5 normal dogs. Death ensued 3 to 5 hours after ligation.

Twelve dogs with supradiaphragmatic constriction of the inferior vena cava were also subjected to division of the portal vein. Six of these survived beyond the 24 hours used as an index for survival. One dog expired after 18 hours. The remaining 5 dogs died within varying periods up to 6 hours after ligation.

Various amounts of ascitic fluid were collected from constricted dogs and no correlation between quantity and survival was noted.

A greater lapse of time between caval constriction and portal vein ligation was noted for survivors (mean 5.3 months) than nonsurvivors (mean 3 months).

In all constricted dogs that survived portal vein division portography revealed the presence of portosystemic collaterals (Figs. 2 and 3).

DISCUSSION

Acute ligation of the portal vein is uniformly fatal in the normal dog. The rapid development of shock following this procedure results from the pooling of blood in the splanchnic bed with decreased circulating blood volume and a reduced cardiac output. This train of events occurs in all animals in which the splanchnic bed is functionally a closed system and whose only communication with systemic circulation is through the liver. In birds, which have an open hepatic portal system, acute ligation of the portal vein is tolerated without difficulty. Gradual occlusion of the portal vein on the other hand is compatible with survival, as Neuhof has shown. This occurs because of the development of adequate portosystemic collaterals capable of returning splanchnic blood to the systemic circulation. The

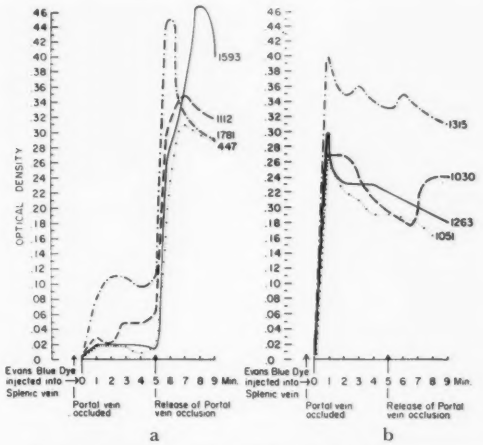

FIG. 1. Appearance of Evans blue dye in the systemic circulation of: a, normal dogs, and, b, dogs in which supradiaphragmatic constriction of the inferior vena cava had been performed.

formation of portosystemic collaterals can be stimulated in other ways to protect the animal from shock after acute ligation of the portal vein. Hoffman and Freidland have shown that transposition of the spleen above the diaphragm causes the establishment of an adequate collateral circulation. The functional significance of portosystemic collaterals in the constricted dog has not been established. Canter and associates and Stewart and associates, using different techniques, have shown that hepatic blood flow is unchanged after supradiaphragmatic constriction of the inferior vena cava. This fact led the latter author to conclude that portosystemic collaterals were functionally insignificant. We have noted in a previous study (6) that caval constricted dogs were able to maintain arterial blood pressure more successfully than normal dogs in the face of acute portal vein occlusion. It was assumed that splanchnic pooling was minimized in constricted dogs by the presence of adequate portosystemic collaterals. The location of these channels has been established by Johnstone and Boyce and associates as well as ourselves (6).

In the present study, the authors have sought to quantitate the effectiveness of the

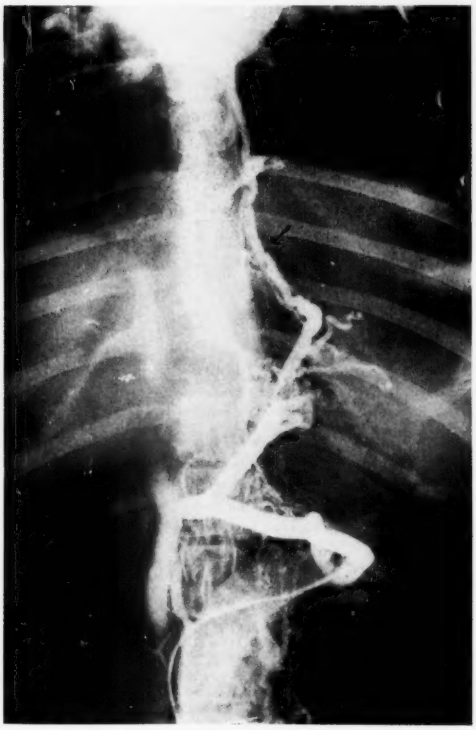

FIG. 2. Dog 1555, 3½ months after caval constriction, anteroposterior view. The portogram demonstrates the passage of radiopaque medium through tortuous vessels along the lesser curvature of the stomach (arrow) and esophagus. The catheter is in the splenic vein.

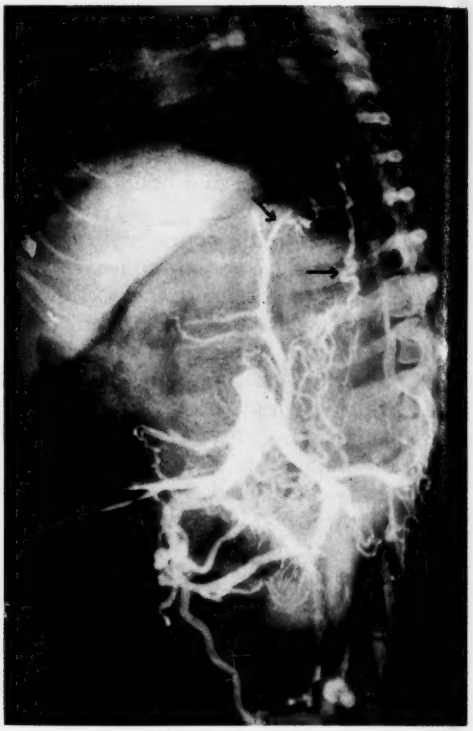

FIG. 3. Dog 1940, 4 months after caval constriction, lateral view. The portogram taken 48 hours after portal vein ligation demonstrates the passage of radiopaque medium into the azygos vein through tortuous vessels along the stomach and esophagus (arrows).

portosystemic shunting of blood in caval constricted dogs as compared with normal dogs.

In the Evans blue dye study, no attempt was made to quantitate the actual collateral flow. However, a marked difference is seen between the dye curves of normal and constricted dogs. In the normal dogs, during the period of portal vein occlusion, little or no dye escapes from the portal bed into the systemic circuit. Upon release of the portal vein, the dye is washed into the systemic circulation. In the constricted dogs, dye injected into the portal bed during portal vein occlusion escapes immediately into the systemic circuit. This fact indicates a marked difference in the ability of collaterals to transport blood from the portal to the systemic circulation. The fact that small amounts of dye appear in the peripheral circulation of normal dogs during portal vein occlusion demonstrates that small collaterals are normally present. In 1 animal which was studied only 4 weeks after caval constriction, a dye appearance curve was obtained which was intermediate between normal dogs and those with long standing caval constriction. Immediately following the dye study, this animal was subjected to ligation and division of the portal vein. This procedure resulted in the appearance of shock and the death of the animal. It is apparent that collaterals of sufficient capacity to return portal blood adequately to the systemic circuit were not present in this animal.

In the small group of normal dogs studied with acute portal vein ligation, our results confirm what has been found by Johnstone. There is rapid appearance of shock and death in all animals. This occurs upon ligation of the portal vein above the gastroduodenal vein. Ligation below that tributary, however, may prolong survival. The present investigators have found that 7 of 12 dogs survived acute portal vein ligation having been previously prepared by supradiaphragmatic constriction of the inferior vena cava. Of 7 survivors, 2 were ligated below the gastroduodenal vein. It is evident that the time elapsed after caval constriction is important for the development of collaterals, although exceptions are noted. Special mention should be made of dog 1386 which was constricted 6 months prior to the present study. This animal survived 18 hours following portal vein ligation. At postmortem examination, this dog resembled survivor dogs. There was no congestion noted in the splanchnic area. Collaterals were seen particularly in the paraesophageal area. Portograms on all survivors consistently demonstrated the passage of radiopaque material from the left gastric vein to dilated paraesophageal veins and thence to the azygos system. The death of dog 1386 can be attributed to the aftereffects of acute massive paracentesis. We have had similar experiences in other experiments in which there were superimposed effects of paracentesis, anesthesia, and surgical trauma. Postmortem findings in normal and constricted dogs which did not survive showed marked congestion of the bowel, mesentery, spleen, and pancreas with blood present in the lumen of the bowel. In the 2 dogs in which the portal vein was ligated below the last tributary, the liver was visualized at subsequent portography. In the other 5 dogs that survived, no contrast medium was seen to enter the liver. Collaterals were visualized in all portograms.

These data support the contention that the formation of portosystemic collaterals is stimulated by caval constriction and that these collaterals are functionally significant. It is also apparent that the collaterals increase in capacity with the passage of time after caval constriction. The fact that portal hypertension is only transient in these animals lends support to the thesis that the portosystemic collaterals decompress this system.

It appears paradoxic that hepatic blood flow should remain constant, portal pressure return toward normal, and portosystemic collaterals increase in functional capacity. We are unable to explain this fact with the evidence currently available. Increased visceral inflow either continuously, or as an intermittently exaggerated response to fac-

TABLE II.—EFFECT OF PORTAL VEIN LIGATION AND DIVISION

Dog No.	*Duration of I.V.C. constriction, months*	*Amount of ascites, ml.*	*Ligation site**	*Postoperative survival*	*Portogram*
			NORMAL DOGS		
854	0	0	Above last tributary	3 hours	0
309	0	0	Above last tributary	3½ hours	0
846	0	0	Above last tributary	4 hours	0
875	0	0	Below last tributary	5 hours	0
1573	0	0	Below last tributary	5 hours	0
			SUPRADIAPHRAGMATIC I.V.C. CONSTRICTED DOGS		
1032	8½	3,000	Above last tributary	Yes	Liver not visualized
1012	8½	100	Above last tributary	No	0
1386	6	9,000	Above last tributary	Yes	0
1419	6	7,000	Above last tributary	Yes	Liver not visualized
1254	5½	7,000	Below last tributary	Yes	Liver visualized
1526	4	3,000	Below last tributary	Yes	Liver visualized
1940	4	3,000	Above last tributary	Yes	Liver not visualized
1555	3½	10,000	Above last tributary	Yes	Liver not visualized
1681	3½	2,000	Above last tributary	No	0
1846	2	3,000	Above last tributary	No	0
1918	1	3,000	Above last tributary	No	0
1881	3 wks.	1,000	Above last tributary	No	0

*Ligation site verified at postmortem examination.

tors normally changing splanchnic flow, may explain it.

SUMMARY

1. Two series of experiments were performed on normal and supradiaphragmatic inferior vena caval constricted dogs in order to evaluate the development of portosystemic collaterals.

2. In the first series, 4 normal and 4 caval constricted dogs were studied. Evans blue dye was injected into the portal bed after acute portal vein occlusion. The rate of appearance of dye in the systemic circulation was noted during occlusion and upon release of the portal vein. In the second series, 5 normal and 12 caval constricted dogs were studied. Acute ligation and division of the portal vein was performed at the porta hepatis.

3. In normal dogs, virtually no dye which had been injected into the portal bed during occlusion of the portal vein appeared in the systemic circuit until release of the portal vein. In constricted dogs, dye immediately appeared in the systemic circuit during portal vein occlusion. Division of the portal vein in normal dogs uniformly resulted in their death within 5 hours. In constricted dogs, however, 7 of 12 survived at least 24 hours.

4. The marked difference in dye curves between normal and constricted dogs as well as the difference in survival upon acute ligation of the portal vein indicate the presence of capable portosystemic collaterals in the constricted dog.

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AN APPRAISAL OF RENAL FUNCTION AND INFECTION IN ADVANCED BLADDER CANCER TREATED WITH ILEAL BLADDER CONSTRUCTION AND IRRADIATION

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EXTENSIVE CARCINOMAS of the urinary bladder commonly present serious medical complications in the form of urinary tract infection and reduced renal function, secondary to partial or complete ureteric obstruction. We have completed a preliminary study of the value of diverting the urinary stream into an isolated loop of ileum as a part of the planned radiation treatment in patients with clinically advanced carcinomas of the urinary bladder.

This investigation was based on 17 patients who were clinically classified as stage C or D before treatment was instituted; bladder carcinoma invading the perivesicle tissue is stage C while tumor invading adjacent pelvic organs or lymph nodes is stage D, according to the classification used by Marshall and Whitmore. Clinical staging was determined at pelvic examination under anesthesia or abdominal laparotomy. All of these were undifferentiated carcinomas, grades III and IV.

The first 8 patients of this group were treated by 6,400 to 7,200 roentgens of 2 million electron volt roentgen rays delivered in 6 to 8 weeks with no attempted diversion of the urinary stream prior to initiation of roentgen ray therapy. Two of these patients had one nonfunctional kidney, on intravenous pyelographic study, and a proved urinary tract infection before radiation therapy was commenced. Five and 7 weeks after treatment—7,200 roentgens in 48 days and 6,600 roentgens in 42 days—acute renal infection and failure developed in these 2 patients, which were not controlled by active medical and surgical procedures, and they died. Postmortem examination revealed acute and chronic pyelonephritis and ureteric obstruction due to edema in the trigone region; there was no gross or microscopic evidence of tumor in the pelvis, although 1 patient did have metastases beyond the pelvis. Of this same group of 8 cases, progressive renal failure due to ureteric obstruction developed in 2 patients at 1 month and 8 months after x-irradiation. These were our first 2 patients to have construction of an ileal bladder. After this procedure, the intravenous pyelogram and blood urea nitrogen indicated prompt and sharp improvement in renal function. One of these patients remains symptom-free and without evident tumor 34 months after therapy. The other patient died 21 months after treatment because of widespread metastatic tumor but without further bladder or renal complications or symptoms. In the terminal phase of his disease, an episode of acute pyelonephritis developed. There was microscopic evidence of residual tumor in the bladder wall on postmortem study. Of the remaining 4 patients in this first group, 1 is alive and symptom-free 28 months after treatment (he had normal renal function as measured by the blood urea nitrogen and intravenous pyelogram, but a urinary tract infection at time of therapy); 3 are known to have died with metastatic tumor at 4, 4, and 10 months after treatment. In brief, of a group of 8 patients with advanced vesicle cancer, 2 fatal and 2 serious nonfatal acute

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TABLE I.—RESULTS OF TREATMENT IN 9 PATIENTS WITH STAGE C OR D BLADDER CARCINOMA AND ILEAL BLADDER CONSTRUCTED BEFORE INITIATION OF ROENTGENOTHERAPY

Case No.	*Stage*	*Dose*	*Symptom control*	*Bladder tumor*	*Current status*
1	C	7500r/ 55d	+	Resolved	Alive and well at 25 months
2	C	7000r/ 51d	+	Resolved	Dead—metastases
3	C	7000r/ 55d	+	Resolved	Dead—metastases
4	C	7000r/ 51d	+	Partial regression	Dead—metastases
5[1]	D_1	7000r/ 50d	+	Partial regression	Dead—metastases
6	C	7500r/ 53d	+	Partial regression	Dead—metastases
7[2]	C	3400r/ 24d	−	Partial regression	Dead—metastases
8[3]	C	5000r/ 68d	+	Partial regression	Dead—metastases
9[4]	D_2	3250r/ 17d	+	Partial regression	Dead—metastases

[1]Proved pelvic lymph node metastases at time of operation for ileal bladder.
[2]Died of cerebral hemorrhage during treatment course.
[3]Skeletal metastases developed during treatment.
[4]Periaortic lymph node metastases found at operation for ileal bladder.

upper urinary tract complications developed shortly after a course of radical roentgen ray therapy. Following this experience the urinary stream has been diverted into an ileal bladder, a modification of Bricker's procedure (4), before initiating roentgenotherapy. We have treated 9 patients according to this plan.

RESULTS OF ROENTGENOTHERAPY AFTER DIVERSION OF THE URINE STREAM

In 9 patients the urinary stream was diverted into an ileal bladder before roentgenotherapy was begun. Hematuria was a prominent symptom in all of the 9 cases. In 8 patients symptoms of urgency, dysuria, and frequency were present and of moderate or marked severity. In addition to the correction of ureteric obstruction, diversion of the urinary stream into an isolated loop of ileum promptly relieved the distressing symptoms of dysuria and frequency, and to a lesser extent the hematuria. The operative procedure afforded the opportunity of more carefully assessing the extent of extravesicle tumor. One patient was found to have metastases to the periaortic nodes and was consequently given a simpler and less intense course of radiation therapy.

High dose roentgenotherapy—7,000 roentgens in 7 weeks—to the whole of the bladder was readily tolerated symptomatically by these patients who had an ileal bladder at the time of treatment. The radiation reaction in the bladder passed unnoticed. This was in sharp contrast to the distressing symptoms noted in the 8 patients whose urinary stream had not been diverted. Six of the 9 patients in the second group received the planned course of treatment: 5,000 roentgens in 5 weeks to the entire pelvic contents by means of a pair of parallel opposed 15 by 15 centimeter fields, followed by 2,000 to 2,500 roentgens in 2 to 2½ weeks, to the residual mass in the bladder, given by either a pair of anterior angled wedge fields or by 270 degree arc rotation using an 8 by 8 centimeter or 10 by 10 centimeter field. All patients were treated with a 2 million electron volt roentgen beam—12 millimeter copper half-value layer—at 100 to 120 centimeters skin target distance. Associated with the ileal bladder were two technical problems. First, the stoma of the ileal bladder was in all cases in the upper outermost portion of the treatment field; this corner of the anterior field was shielded from the roentgen rays by lead. Second, a portion of the ileal loop fell into the uppermost position of the treated zone; however, a maximum dose to this segment of ileum would have been 5,000 roentgens or less. In no instance did symptoms develop which were attributable to the irradiation of the ileal bladder.

Although survival periods have been short, the combined treatment has been effective in relieving bladder symptoms from the time of treatment to either the last follow-up examination or death of the patient. Urgency, frequency, and burning almost completely disappeared after the diversion of the urinary system. Hematuria was controlled in all cases by the irradiation, and

TABLE II.—SITE OF TUMOR, URINE CULTURE, BLOOD UREA NITROGEN AND INTRAVENOUS PYELOGRAPHIC STUDIES BEFORE AND 2 MONTHS AFTER ILEAL BLADDER CONSTRUCTION IN 11 PATIENTS WITH STAGE C OR D BLADDER CANCER

		Before ileal bladder construction			*2 months after ileal bladder construction*		
Case No.	*Site of tumor*	*Urine cult. $\geq 10^4$ colonies/c.c.*	*BUN, mgm. per cent*	*IVP R/L*	*Urine cult. $\geq 10^4$ colonies/c.c.*	*BUN, mgm. per cent*	*IVP R/L*
1	Lt. wall trigone	+	25	H/NF	+	20	N/N
2	Dome	+	7	N/N	+	15	N/H
3	Rt. wall trigone	+	10	H/N	+	9	H/N
4	Rt. wall	−	15	N/N	−	15	N/N
5	Rt. wall base trigone	+	8	H/H	+	12	H/N
6	Rt. wall base trigone	−	12	NF/H	+	12	N/N
7	Rt. and lt. wall base trigone	+	17	NF/N	+	13	NF/H
8	Base trigone	+	72	H/H	+	11	H/H
9	Base trigone	+	15	H/NF	+	—	N/N
10	Rt. wall base	+	16	H/H	+	14	N/N
11	Lt. wall trigone	+	31	N/NF	+	16	—

N, normal; H, definite hydronephrosis; NF, nonfunctioning kidney.

there were no symptoms of cystitis during or after treatment. Thus, these cases had relief of ureteric obstruction, control of the bladder symptoms, and an asymptomatic course of roentgenotherapy. Results of treatment in these cases are presented in Table I. Two patients had no pelvic tumor at postmortem while the others had some residual carcinoma. One patient had a small recurrence of the bladder tumor 8 months after the x-irradiation; this was treated by a transvesicle iridium 192 seed implant. After this procedure, a fistula developed through the cystotomy wound. The fistula has now closed, and on cytoscopic examination 9 months after the implant the bladder was well epithelized, and no tumor was evident.

In our group of 9 patients treated by urinary stream diversion followed by x-irradiation, 7 are dead from widespread metastases, while 1 patient had a fatal cerebral hemorrhage during treatment. The other patient remains alive and well 25 months after initial treatment, without evident tumor. There were no fatal renal complications in these patients. Thus 7 of 9 patients died with extensive metastases; the experience is similar to that reported by others. Jewett found metastases in 15 of 18 patients with undifferentiated carcinoma, stage C, that were studied at postmortem.

RENAL FUNCTION AND URINE BACTERIOLOGIC STUDIES

Including the 2 patients for whom an ileal bladder was formed to relieve ureteric obstruction developing after roentgenotherapy, we have studied renal function and the urine bacteria before and after construction of an ileal bladder in 11 cases of stage C and D bladder carcinomas. Table II shows the site of tumor, urine culture findings, blood urea nitrogen, and intravenous pyelographic studies before and 2 months after the construction of an ileal bladder. With the exception of 2 cases, all patients had significant bacteriuria when first seen and in nearly all subsequent urine cultures. A total of 82 urine cultures were taken in these 11 patients; 65 had bacterial colony counts $\geq 10^4$ bacteria per cubic centimeter, while 5 urine samples were reported as showing "no growth." Cultures were obtained directly from the ileal bladder with a catheter tip following routine antiseptic technique. Figure 1 demonstrates that the bacterial colony

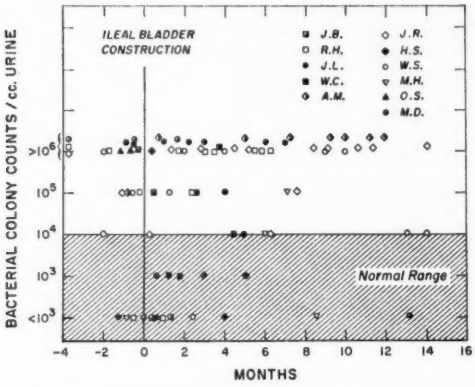

FIG. 1. Quantitative urine cultures in relationship to ileal bladder construction.

counts of the urine did not change remarkably after the diversion of the urinary stream and that there was persistent bacteriuria, despite ileal bladder construction and appropriate antibiotic therapy.

A variety of bacteria were cultured from these patients, and on many occasions several pathogenic organisms were found in a single urine sample. The spectrum of the pathogenic organisms was not changed by ileal bladder construction or antibiotic therapy.

The presence of Candida albicans—which occurred at some time during the postoperative period in every patient—and of Streptococcus faecalis was not related to general clinical status, episodes of acute pyelonephritis, or antibiotic treatment. In no urine culture showing significant bacterial colony counts were candida or streptococcus the only organisms present, and all episodes of acute pyelonephritis were due to gram negative organisms.

Of the 11 patients in this group, 7 had 1 or more episodes of acute pyelonephritis before the ileal bladder was formed. Four of these 7 patients had no further bouts of acute renal infection after diversion of the urinary stream; in 2 of these 4 it is now 34 and 25 months after operation. However, 2 patients had their initial clinical episode of acute pyelonephritis after the ileal bladder was established; in neither instance was there evidence of ureteral or stomal obstruction. These 2 patients responded clinically to aggressive antimicrobial therapy. All 6 patients on whom postmortem material was available showed chronic pyelonephritis. The patient (Case 4) who almost consistently had insignificant urine bacterial counts throughout the disease had only "minimal" chronic pyelonephritis at postmortem examination.

Clinical episodes of acute pyelonephritis occurred in 5 patients after diversion of the urinary stream. Three of these were examined by necropsy at this institution, and each had both acute and chronic pyelonephritis. These 3 patients had evidence of renal infection during the terminal phase of the disease, at which time there was evidence of diffuse metastases and failing renal function but no signs or symptoms of urinary tract obstruction. It is interesting to note that the 3 patients without clinical evidence of acute pyelonephritis postoperatively and in whom autopsies were obtained here did not show evidence of acute pyelonephritis pathologically.

Estimations of renal function by blood urea nitrogen, serum creatinine, and intravenous pyelographic examination indicated a prompt and rather striking return toward normal after the ileal bladder was constructed when abnormality was present beforehand. This observation is in agreement with those in other series. However, more sensitive indicators of renal function are the endogenous creatinine clearance and fractional phenolsulfonphthalein excretion studies. All of our patients studied by these tests demonstrated markedly depressed creatinine clearance rates and phenolsulfonphthalein excretion including those with normal blood urea nitrogen, serum creatinine, and intravenous pyelograms. In our cases, despite obvious clinical improvement and a return to normal or near normal of the blood urea nitrogen and intravenous pyelogram, the creatinine clearance remained severely depressed. Figure 2 shows

the lack of definite improvement in creatinine clearance after the ureteric obstruction was relieved while serum creatinine returned to normal or near normal levels (Fig. 3). The 15 minute and 30 minute phenolsulfonphthalein excretion values did not return to normal (Figs. 4 and 5). The blood urea nitrogen and serum creatinine levels did not correlate with the creatinine clearance or phenolsulfonphthalein excretion.

DISCUSSION

Patients in whom the urinary stream has been diverted into an isolated loop of ileum because of advanced lower urinary obstruction and failing function provide interesting material for the study of renal function and infection. The long term effects of urinary stream diversion are still unknown, as is the pathogenesis of pyelonephritis. Urinary tract obstruction, bladder infection, instrumentation, and ureteral reflux (factors which according to Beeson play some role in the pathogenesis of pyelonephritis) were all present in some stage of the clinical course of our patients. Five of our 11 patients had 1 nonfunctional kidney prior to the formation of the ileal bladder. Bricker (5) has reported the late results in 28 patients who have had ileal bladder construction. Eight of these patients, who were followed up for more than 6 months, had episodes of acute pyelonephritis. In a later report (6), 8 of 65 patients followed up for periods of longer than 6 months had episodes of acute pyelonephritis. He could demonstrate no correlation between hydronephrosis and postoperative episodes of acute pyelonephritis in a 6 to 36 month follow-up period. Nine patients had hydronephrosis without pyelonephritis; 8 patients had pyelonephritis without hydronephrosis, and only 4 patients had both. Renal status, as indicated by the nonprotein nitrogen, lack of clinical pyelonephritis, and intravenous pyelograms was satisfactory in 87 per cent of his patients. Jude and his associates have

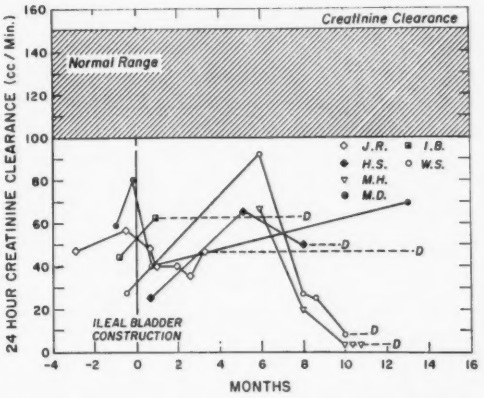

FIG. 2. Temporal relationship between ileal bladder construction and renal function—creatinine clearance. The interrupted line indicates the elapsed time between the last determination and the death of the patient.

also studied renal function in similar cases. Postoperatively, they noted that in approximately 90 per cent of their patients the 2 hour phenolsulfonphthalein excretion, serum creatinine, and blood urea nitrogen were within normal limits. There was no evidence of pyelonephritis occurring in the absence of urinary tract obstruction. Kidney function as estimated by these measures remained good or improved subsequent to ileal bladder construction. Murphy and associates noted rapid improvement of renal function after diversion of the urinary

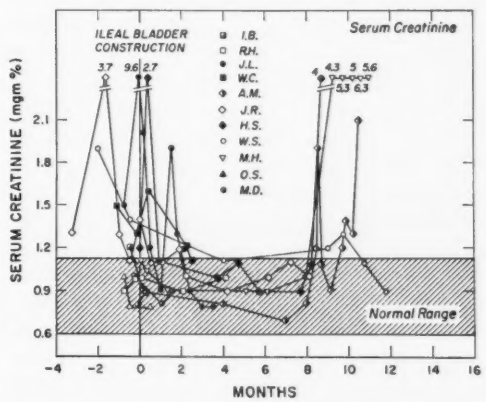

FIG. 3. Temporal relationship between ileal bladder construction and renal function—serum creatinine levels.

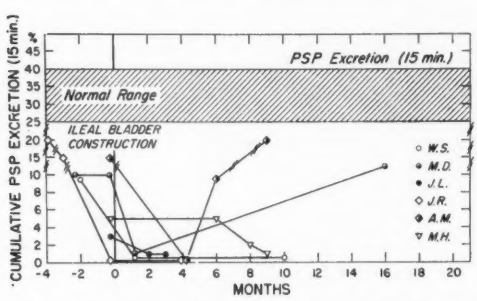

FIG. 4. Temporal relationship between ileal bladder construction and renal function—phenolsulfonphthalein excretion in 15 minutes.

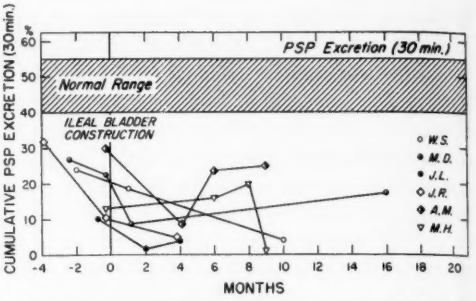

FIG. 5. Temporal relationship between ileal bladder construction and renal function—phenolsulfonphthalein excretion in 30 minutes.

stream, as measured by the blood urea nitrogen and intravenous pyelography. With the exception of 1 case in their series of 22, there were no episodes of pyelonephritis and "none had progressive renal impairment." The lone dissenting comment heretofore has been that of Miles and Berry who state "the complication that most commonly occurs after urinary tract diversion in pyelonephritis." They report that virtually all of their 110 patients had an upper urinary tract infection although no bacteriological data are presented.

In our studies, we have selected the quantitative urine culture, endogenous creatinine clearance, and 15 minute and 30 minute phenolsulfonphthalein excretion tests to indicate the extent of bacteriuria and impairment of renal function. The endogenous creatinine clearance has been shown in man to be a valid measure of glomerular filtration. Camera and associates believed that the 24 hour endogenous creatinine clearance was a good measure of the functional state of the kidneys. His group of patients included 4 with normal serum creatinine levels but with significantly decreased creatinine clearance. Bradley and associates noted a decrease in the glomerular filtration rate in all of 4 patients with chronic pyelonephritis. They believed that these patients demonstrated more tubular than glomerular damage, and that the glomerular filtration and renal blood flow were maintained until relatively late in the course of the disease. Arkin and associates believed that the plasma creatinine determination could be used to demonstrate low grade kidney damage and reported that in 9 patients with pyelitis, 3 had an elevated plasma creatinine.

The use of quantitative urine cultures in the evaluation of upper urinary tract infection has been well established. In an interesting article, MacDonald and associates correlated clinical impressions with postmortem findings. Ten of the 14 patients who had a diagnosis of genitourinary tract infection had bacterial colony counts of greater than 10^5 colonies per cubic centimeter. Six of these 10 patients had acute pyelonephritis at postmortem examination. However, only 6 of 20 patients who were found at postmortem examination to have acute pyelonephritis were diagnosed clinically. Thus, the problem of diagnosing chronic pyelonephritis is still not solved, and the problem of "asymptomatic bacteriuria" is far from settled.

Kipnis and Chait and their associates, in attempting to correlate renal function with morphology, also noted apparent discrepancies in their data and Chait concluded that "important functional and structural changes of the kidney can be present with minor or no clinical evidence and without proper substantiation by means of the usual clinical investigation."

We were particularly interested to learn that our patients with severe depression of

creatinine clearance and of the 15 and 30 minute phenolsulfonphthalein excretion levels, persisting after the ileal bladder was functioning well, had normal or near normal serum creatinine, blood urea nitrogen, and intravenous pyelographic studies. This divergence of data was maintained until shortly before death of the patients. Actually, there was often a further gradual decline in the creatinine clearance and phenolsulfonphthalein excretion while the serum creatinine remained relatively constant. Phenolsulfonphthalein excretion at 15 and 30 minutes was almost always below 50 per cent of normal, and in no instance was greater than 60 per cent of normal. In no case did any patient subsequent to operation demonstrate normal levels of phenolsulfonphthalein excretion or creatinine clearance.

Effersoe has noted that a very slight increase in serum creatinine concentration is compatible with a great decrease in renal function. He reported that the serum creatinine concentration, in the face of decreasing renal function, might rise much less than would be expected. Goldman expressed a similar opinion and, while noting that remarkably low serum creatinine concentrations were found with low creatinine clearances, could not account for this divergence of data by weight loss nor by the loss of creatinine or creatine in the feces. Effersoe and Goldman both raised the question of decreased creatinine production in renal failure. While this has not been established, it would account for our findings. Kleeman and associates, in a recent review dealing with chronic pyelonephritis, state that the creatinine clearance often decreases more than one would assume by following only the serum creatinine.

In addition to the poor functional status of the kidneys, no important change in the bacterial colony counts or in the types of organisms present was found in the postoperative periods. These data suggest to us that the damage to the kidneys from prolonged urinary tract infection and ureteral obstruction of varying degree and duration may not be corrected by relief of urinary tract obstruction and that the extent of bacteriuria remains unaltered. Despite this discouraging finding, we believe that the ileal bladder, by relieving the ureteric obstruction, at least retarded the development of additional renal damage. In addition, the procedure was of real symptomatic benefit to the patient and greatly facilitated the radiation therapy.

SUMMARY

Eleven patients with advanced bladder cancer who have had ileal bladder construction and x-irradiation therapy have been studied before and after operation with respect to renal function and infection. Renal function as measured by 15 minute and 30 minute phenolsulfonphthalein excretion and creatinine clearance was found to be sharply depressed before and after formation of an ileal bladder even though the blood urea nitrogen, serum creatinine, and intravenous pyelograms markedly improved in the postoperative period. There was no change in the quantitative urine cultures during this same time. There was no instance of urinary tract obstruction or involvement of kidney by tumor in our patients at postmortem examination. Our data indicate renal function is more compromised in these patients than had been appreciated previously. Urinary stream diversion was not noted to cause any significant improvement in renal function as measured by the endogenous creatinine clearance and fractional phenolsulfonphthalein excretion, or to effect a change in urine bacteriology. However, this procedure was quite effective in providing prompt relief of the distressing symptoms of bladder cancer and it did facilitate the radiation therapy of the extensive bladder tumor and the control of acute infection of the upper urinary tract.

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COMPARATIVE LONG TERM STUDY FOLLOWING PULMONARY RESECTION FOR TUBERCULOSIS

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IT IS GENERALLY RECOGNIZED that the hazards of pulmonary resection for tuberculosis are increased if operation is performed in the presence of a persistently positive sputum. The immediate postoperative complication rate is measurably increased and the immediate results in most series are not as good in the positive cases as they are in cases that are negative at the time of resection. These facts have been well documented in studies by Raleigh and Steele from the Veterans Administration and by other investigators. The reasons that these observations are true may seem obvious enough on the surface, but closer study makes it evident that there may be other important factors involved besides the mere presence of a persistently positive sputum. In fact, the positive sputum frequently indicates more important and serious connotations than would at first be suspected. If the presence of a positive sputum constituted the only important difference between the positive and negative groups, one would surmise that each might do equally well once they had survived successfully the immediate postoperative period and recovered from any immediate postoperative complications.

MATERIAL

A survey was undertaken to determine the long term results of a positive group and to determine what factors were responsible for any differences that might be observed between this group and a negative group. From 1952 through 1958, a 7 year period, 475 pulmonary resections for tuberculosis were performed at the North Carolina Sanatorium in McCain, North Carolina, as reported by Floyd and associates. These resections were performed by 16 surgical residents from the Duke University Medical Center under the supervision of William F. Hollister. In that 7 year period, of 66 patients 36 had a positive smear, and 30 patients a positive culture for Mycobacterium tuberculosis within 3 months prior to surgery, or 13.9 per cent of the entire group. For purposes of comparison, a survey was made of all the patients having resection in the 2 years 1954 and 1957 who had a negative sputum at least 3 months prior to surgery. These 2 years were picked at random. There were 133 such cases. This latter group will be referred to as the negative group and those with a positive sputum at the time of operation will be referred to as the positive group.

The positive group was followed up from 6 months to 8 years, with an average of 42 months or 3½ years; 95 per cent of the follow-ups were for more than 1 year. The negative group was followed up from 6 months to 5½ years with an average of 3½ years also; 85 per cent of the follow-ups were for more than 1 year. In getting these follow-up statistics, we have had excellent co-operation from the various county health departments and the other sanatoria throughout North Carolina and from other states.

SIGNIFICANT DATA

The average age, 35 to 36 years, was approximately the same in the 2 groups. There

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were 64 per cent males in the positive and 54 per cent males in the negative group. It is interesting that more white patients were in the positive group, 69 per cent, than in the negative group, 49 per cent; although the number of Negro patients admitted to the sanatorium exceeds the white.

At the time of admission to the sanatorium, only 27 per cent of the positive group had minimal tuberculosis, whereas 14 per cent of the negative group were minimal. Originally, 28 per cent of the positive group had moderately advanced disease and 70 per cent had far advanced disease as compared with 44 per cent and 42 per cent, respectively, for the negative group.

The extent of resection was greater in the positive group, as would be expected from the original severity of the disease as mentioned: 4 per cent of patients in the positive group had a wedge resection as compared with 9 per cent of those in the negative group. A segmental resection was performed in 18 per cent of the positive and in 21 per cent of the negative group patients, a lobectomy in 60 per cent of the positive and 63 per cent of the negative group patients, and a pneumonectomy in 18 per cent of members of the positive group, but in only 7 per cent of the negative group members.

Of the positive group all patients had 2 or more of the major antituberculous drugs, streptomycin, isoniazid, and para-aminosalicylic acid, and many had all 3 major drugs and 1 or more of the 3 minor drugs, cycloserine, pyrazinamide, and viomycin. Some patients had all 6 drugs. After early 1953, most members of the positive group had 3 or more drugs. Only 55 per cent of the positive group members had an uninterrupted course of chemotherapy prior to surgery, this being for an average duration of 16 months. The other 45 per cent had an interrupted course of chemotherapy for an average total of 22 months. Drug resistance is assumed in all of the patients with positive sputum, in that the sputum remained positive despite adequate antituberculous drug therapy and laboratory sensitivity studies in some cases to the contrary. Sensitivity studies were available in 76 per cent of the positive group. Only 42 per cent of those studied were resistant to streptomycin in the strongest concentration used, 64 per cent to isoniazid, 49 per cent to para-aminosalicylic acid, and only 20 per cent to all of the drugs studied. All in the positive group had one or more additional drugs over and above those to which their organisms were resistant, yet had positive sputum.

One of the most interesting facets of the entire study was the irregular discharge rate in the two groups. In the positive group, 56 per cent left the sanatorium against medical advice from one to three times, either before or after surgery, or both. Approximately one-half these patients re-entered the sanatorium of their own volition, whereas approximately 25 per cent of the entire group required apprehension by law enforcement authorities and were admitted to the prison division of the sanatorium through legal means as violators of the North Carolina Health Law. In the negative group, only 10 per cent of the patients left the sanatorium one or more times on irregular discharge, and less than 5 per cent were health law violators. The over-all irregular discharge rate at the North Carolina Sanatorium is less than 10 per cent.

Ninety-one per cent of the indications for resection in the positive group comprised persistent cavity, destroyed lung, residual fibrocaseous disease, and failure of thoracoplasty or plombage. Fifty per cent of the patients had a right thoracotomy and 52 per cent had a left thoracotomy, 1 patient having a planned bilateral resection. Fifty-two per cent had had collapse therapy of one type or another prior to resectional surgery, 25 per cent of the entire positive group having permanent physiologic derangement to the thorax prior to resection, either by pneumothorax, phrenic nerve crush, thoracoplasty, or plombage. The onset of symptoms in the positive group antedated resectional surgery for an average of 4 years. There seems to be no trend in the annual

number of resections performed at the North Carolina Sanatorium upon patients whose sputum was positive at the time of surgery.

DEFINITIONS

The same terminology will be used in presenting the results as was used by Floyd and associates.

Bronchopleural fistula. This is the development of an air or air-fluid level in the pleural cavity signified the presence of a fistula. Often this fistula was accompanied with expectoration of old blood. Also, a fistula was present if air continued to leak via the intercostal catheter for more than 10 to 14 days and if an increasing pleural air space developed on clamping or removing the intercostal tube.

Space problem. This term is used to describe the space in the hemithorax that the remaining lung failed to fill after resection. When a space problem was associated with a bronchopleural fistula, the latter term was used to describe the condition.

Hemothorax. Patients with obliteration of one-fourth or more of the hemithorax by clotted blood were considered to have postoperative hemothorax.

Disease spread. Irrespective of a patient's postoperative course, the spread of tuberculosis was determined by changes in the roentgen films, along with a positive sputum by smear or culture.

Early death. This was construed as death within 30 days of pulmonary resection.

Late death. Death occurring more than 30 days after pulmonary resection was considered to be late death. It so happened that all of these deaths occurred 3 months or more after resection.

RESULTS

Of the 66 patients with positive sputum, 73 per cent were alive and free of disease at the time of their last follow-up examination and all of these patients were at home, working or able to work. Ten per cent of the positive group still had positive sputum, and 17 per cent were dead.

Of the 133 patients with negative sputum, 90 per cent were at home, working or able to work, and their sputum was still negative at the time of their last follow-up examination. There were no relapses in this entire group. Ten per cent of the patients were dead but none of them died of tuberculosis or a direct complication thereof.

There were 11 deaths in the positive group, 17 per cent. Five were early deaths and 6 were late deaths. All of the 5 early, or surgical, deaths followed pneumonectomies. Two patients died of respiratory insufficiency in 1952. It is interesting that since the advent of careful pulmonary function studies, we have had no deaths due to respiratory insufficiency in this group. One of the 5 expired on the operating table from exsanguinating hemorrhage from the superior vena cava. This patient had had a previous thoracoplasty. A fourth patient died of a massive cerebral hemorrhage 20 days postoperatively, and the fifth patient expired of contralateral spread of disease with overwhelming pneumonia. Six other patients expired from 3 months to 6½ years after operation. One of these patients probably had a myocardial infarction, although the exact cause of death is unknown. He had been examined 1 month previously and had been found to be free of tuberculosis. The other 5 patients had spread of disease and 1 had nontuberculous empyema. Thus, 6 patients in the positive group have died of spread of disease, 4 of these patients having bronchopleural fistulas. Two died of respiratory insufficiency, 2 of vascular disease, and 1 because of a technical surgical problem. Death from tuberculosis or direct complications thereof was 9 per cent and from other causes, 8 per cent. There were 13 deaths in the negative group, or 10 per cent. There were 3 surgical deaths, 2 from pulmonary embolism and 1 from uncontrolled hemorrhage on the third postoperative day. There were 10 late deaths: 1 from epilepsy, 1 from hypertension, 1 from carcinoma, 1 from pulmonary insufficiency 1 year postoperative, 1 from acute cardiac failure 9 months

after operation when the patient had an incomplete abortion, 1 from myocardial infarction, 1 from an unknown cause, and 3 from nontuberculous pneumonia. There were no deaths attributable to pulmonary tuberculosis in this negative group of patients.

The over-all results in the positive group were analyzed in another manner, dividing the patients with positive sputum into 2 categories: co-operative and unco-operative, the latter evidenced by one or more irregular discharges either before or after surgery, or both. As mentioned earlier 56 per cent, or 37 of the patients, with positive sputum fell into the latter category, and it was largely this unco-operative group whose prescribed course of drug therapy was interrupted prior to surgery—the retreatment group. Of this irregularly discharged group of 37 patients, 65 per cent are currently free of disease, while 19 per cent still have positive sputum, 11 per cent are dead as a result of tuberculosis or a direct complication thereof, and 5 per cent are dead of other causes. Of the co-operative group of 35 patients, 83 per cent are now free of disease, none has positive sputum, 7 per cent are dead of tuberculosis or a direct complication thereof, and 10 per cent are dead of other causes. Thus, resectional surgery failed to cure the tuberculosis in the co-operative group in only 7 per cent, as compared to 30 per cent in the irregularly discharged group.

Of Floyd and associates' 430 patients, 370 had a negative sputum. We have compared the complications in 66 patients with positive sputum with those 370 patients with a negative sputum. Thirty-five of 66 in the positive group had significant postoperative complications, or 53 per cent, and there were 5 surgical deaths, or 8 per cent. In the negative group there were 60 complications after 370 resections, or 16 per cent, and 6 deaths, or 1.6 per cent. Spread of disease and bronchopleural fistula appeared to be the most significant complications, accounting for most of the late deaths and the persistently positive sputums after surgery, and were often associated with each other, with hemothorax, or with both. In the positive group there were 7 spreads, 11 per cent, and none in the negative group. There were 16 bronchopleural fistulas, 24 per cent, among the positive group, compared with 33, or 7.1 per cent, in the negative group. Hemothorax occurred postoperatively in 8 patients in the positive group, 12 per cent, and in 10 in the negative group, 2.7 per cent.

The long term follow-up on the patients with positive sputum may be analyzed in relation to their complications. Of the 7 patients whose disease spread to the contralateral lung or ipsilateral remaining lung, 4 with and 3 without associated complications, 6 are now dead and 1 still has positive sputum. Of the 16 in whom a bronchopleural fistula developed, 6 with and 10 without affiliated complications, 4 are dead, 5 still have positive, and 7 have negative sputum. Of 8 patients in whom a hemothorax developed, 4 with and 4 without associated complications, 2 are dead, 2 still have positive, and 4 have negative sputum; these latter 4 were without associated complications. The 5 patients listed as having space problems all had a relatively small space requiring no surgical therapy. All of them are now negative. All those who had a large space went on to development of bronchopleural fistula or already had one and have been covered under that particular topic.

Thus, of 35 patients who had 41 complications, 10 are now dead, 7 are still positive, and 18 are now negative. Of the 31 patients who had an uneventful postoperative course, 1 is dead, probably of a myocardial infarction, and 30 have negative sputum; none has become reactivated.

The follow-up examination on patients with a preoperative positive sputum who died or remained positive was analyzed as to drug resistance as measured by bacteriologic study. Of the 13 patients with poor results, 6 were resistant or partially resistant to all antituberculous drugs tested. All of these patients had from 1 to 3 drugs preopera-

tively over and above the drug or drugs to which their organisms were found to be resistant. Four other patients with positive sputum had organisms resistant to all of the drugs tested but have had a satisfactory result.

Of the 66 patients who had a positive sputum within 3 months prior to pulmonary resection, 36 of them, or 55 per cent, were positive on direct smear, while the other 30 patients, or 45 per cent, had a negative smear but a positive culture. Obviously, the patients with a positive smear were a definitely poor risk group, accounting for 9 of the 13 poor results, or 69 per cent. Of the 6 postresection deaths due to pulmonary tuberculosis or a direct complication thereof, 5 of the patients, or 83 per cent, had a positive smear preoperatively. Of the 7 patients who were still positive on late follow-up examination, 4, or 57 per cent, were positive on direct smear preoperatively.

DISCUSSION

Prior to 1943, there had been 83 pulmonary resections for tuberculosis, as reported by Thornton and Adams. Only 15 of the reported patients were known to have a positive sputum prior to surgery; 7 of these patients with resection had a satisfactory result without the advantages of antituberculous chemotherapy, 46 per cent, 1 had an unsatisfactory result, and 7 died. In 1946 Sweet reported 27 lobectomies and 36 pneumonectomies for tuberculosis, with at least 1 year elapsing since surgery. Forty-eight per cent of the patients with lobectomies and 45 per cent of those with pneumonectomies had a satisfactory result. None of these patients had streptomycin; we do not know the status of their preoperative sputum studies but we must assume that the majority of them were positive. Overholt and associates, in 1946, reported a 2 year follow-up study of 33 lobectomies and 56 pneumonectomies for tuberculosis without drug coverage, in which 85 per cent of the patients had positive sputum. The results in these patients were similar to those of Sweet, satisfactory in 40 per cent of the patients with lobectomies and in 43 per cent of those with pneumonectomies. Strieder, in discussing the papers by Sweet and Overholt and co-workers, stated that 60 per cent of his 10 patients with lobectomies had spread of disease and 10 per cent had died, leaving a satisfactory result in 30 per cent of a small group of 10 patients; of 13 with pneumonectomies, 45 per cent had spread of disease and 23 had died, leaving a satisfactory result in 32 per cent. If all of these cases are added together, we find that satisfactory results were obtained in 80 of these 190 patients with resections for pulmonary tuberculosis in the prestreptomycin era, or 42 per cent. It is rather difficult to assess the differences in results between the preoperatively positive and negative groups in the earlier literature, in that little emphasis was placed on the results in comparative studies. In fact, even the Veterans Administration, in their comprehensive analyses, did not list the preoperative sputum status of the patients prior to the report by Decker and Wade in 1957. Our findings showed the results to be satisfactory in 90 per cent of the negative and 73 per cent of the positive group. Moreover, in the positive group, 83 per cent of the cooperative group, undergoing original treatment, as compared to only 65 per cent of the unco-operative group, undergoing retreatment, showed satisfactory results. Holland and associates reported a similar trend.

SUMMARY

The over-all results of pulmonary resection for tuberculosis, with an average 3½ year follow-up, are presented in 66 patients with a positive sputum within 3 months prior to operation and in 133 patients with a negative sputum.

Seventy-three per cent in the positive, and 90 per cent in the negative group had a satisfactory result.

Indication for, and extent of, resection, preoperative drug therapy and resistance, irregular discharges from the sanatorium,

complications, and the effect of these various factors on the over-all results have been emphasized.

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TREATMENT OF ACUTE HYPERKALEMIA UTILIZING EXTRACORPOREAL PERFUSION OF BLOOD THROUGH CATION EXCHANGE RESIN COLUMNS

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IN THE TREATMENT of acute renal failure, the physician is frequently faced with a sudden rise of serum potassium. This may occur when patients have sustained large surface area burns, crush injuries of the extremities, large hematomas, or any other condition resulting in a rapid catabolic state. The cells rapidly become saturated with potassium and the serum level may rise suddenly, resulting in death due to cardiac asystole or arrhythmia.

Currently, the artificial kidney is the most effective device for management of anuric or oliguric patients when conservative methods are inadequate. However, its use has a number of disadvantages: (1) Preparation for a dialysis, and the procedure itself, may be too time-consuming. (2) A permanent team of highly trained personnel is required. (3) The apparatus is bulky, expensive, and requires a special room. (4) Preparation of the solutions requires high volumes of fluid, frequent checks of *p*H, osmolarity, and electrolyte content.

This study was undertaken to evaluate the use of a sodium cycle cation exchange resin for the treatment of acute hyperkalemia, utilizing an extracorporeal pump circuit. This study was carried out both in the laboratory and on human patients.

Resins are a group of compounds which have the facility for exchanging ions. By ion exchange we mean a reversible exchange of ions between a liquid and solid phase with no chemical change of the solid itself, the solid being the resin. Most synthetic resins currently in use are polymerized complex hydrocarbons with many ion active groups. Each of these ion groups is bound with an oppositely charged mobile ion which is free to exchange with other ions of similar charge; for example, Na^+, Mg^{++}, and NH_4^+.

The affinity of an exchange resin for a particular ion depends upon the atomic weight and valence of the ion, there being a greater affinity for ions of higher valence and atomic weight. Thus, for cation exchange resins in the sodium cycle, there would be the greatest affinity for the ions Ca^{++}, Mg^{++}, and K^+, in that order. Affinities for potassium and ammonium ions are approximately the same.

In addition to the ability of resins to exchange ions, there is also a nonspecific effect resulting from dialysis of molecules across a semipermeable membrane. This membrane is formed by the interface between the surface of the resin bead and the water molecules surrounding it. Bronnimann and Pini also described an adsorption phenomenon which occurs upon the resin molecules. Specificity of the molecules adsorbed depends upon the physical and chemical properties of the resin.

Cation exchange resins were first used to treat uremic patients with hyperkalemia by Elkinton and associates. Resins were administered in the form of enemas and oral preparations. It was found that the oral preparations were not well tolerated in uremic patients, but that up to 73 milliequivalents of potassium per liter of enema fluid could be removed. Muirhead and Reid first described the use of cation exchange

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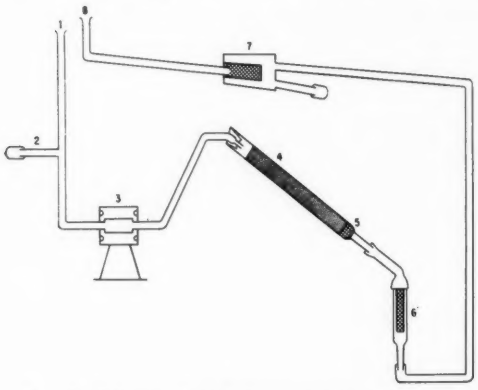


FIG. 1. Schema of perfusion apparatus. *1*, Afferent tube to femoral artery. *2*, Female connector for administering fluids. *3*, Sigma motor pump. *4*, Resin column, 1 inch outside diameter pyrex tube. *5*, Spun glass for resin bed. *6*, Blood filter. *7*, Blood filter with air vent. *8*, Efferent tube to femoral vein.

resins to remove potassium from the blood of previously nephrectomized animals. The animal's blood was percolated through a resin column and returned to the animal. This method was not used clinically. Kessler and associates also described the use of cation exchange resins to remove potassium from the blood of nephrectomized animals by utilizing arterial blood pressure to pump blood through the columns and back into the animal. At flow rates of 30 to 60 milliliters per minute, 90 per cent of the calcium and potassium was removed from the blood

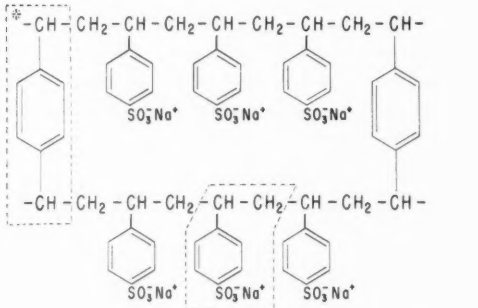


FIG. 2. Structure of polystyrene-divinylbenzene copolymer. The divinylbenzene molecules crosslink with the polymerized styrene, forming a 3 dimensional network.

in one passage through the columns. The calcium and magnesium that were removed were replaced.

Kahn and Emerson and other investigators have used resins orally to control the edema of congestive heart failure. Their goal was to remove sodium, but they also noted that potassium and calcium were lost in significant amounts which required replacement. Schechter and associates (7) recently reported perfusion of blood through vinylite hemorepellent cation exchange resin columns to remove potassium from nephrectomized dogs, using the animal's arterial pressure to propel blood through the columns. It was noted that resin columns were quite efficient in lowering the elevated serum potassium and that the nephrectomized animals survived 2 or 3 days longer than control animals. These same authors (8) also tried this technique to remove ammonium ions in animals with Eck fistulas and reported lowering the blood ammonia level in 1 patient who was in a coma due to hepatic insufficiency. A dramatic clinical improvement was observed. Both Schechter and Kessler observed that there was no hemolysis of the blood after the perfusion.

MATERIALS AND METHODS

Fifteen mongrel dogs weighing from 25 to 60 pounds were used in this experiment. All animals underwent bilateral nephrectomy. Three animals died shortly after operation, either as a result of blood loss or from anesthesia. Six dogs were given a dilute solution of potassium chloride intravenously, 0.1 milliequivalent per cubic centimeter immediately after bilateral nephrectomy. As the potassium was injected the rise in serum potassium was monitored on a continuously running electrocardiogram. The results in these dogs are not reported, as we found that death from cardiac asystole or ventricular fibrillation occurred before there was time to begin the perfusion.

The remaining 6 dogs were studied in the following manner: Approximately 90 hours after bilateral nephrectomy, they were

anesthetized with intravenous sodium nembutal, 60 milligrams per 10 pounds of body weight, and their blood was perfused through the resin columns. Not only was this more successful in terms of immediate animal mortality, but the experimental conditions were thought to more nearly resemble the clinical circumstances of anuria with hyperkalemia. Polyethylene cannulas were placed in the right femoral artery and both femoral veins. One jugular vein and one carotid artery were also cannulated. Blood pressure was measured with a mercury manometer connected to the carotid artery. The jugular vein was used for taking blood samples for chemical determinations. Through the cannula in one of the femoral veins, heparin, 10 milligrams per 10 pounds of body weight, was given, and an infusion of 500 cubic centimeters of 5 per cent dextrose in water, to which was added 1 gram of calcium chloride and 250 milligrams of magnesium sulfate, was run at 15 drops per minute. The contralateral femoral artery and vein were used to connect the afferent and efferent tubing going to and from the resin columns and sigma motor pump. Blood was pumped from the femoral artery, through the perfusion apparatus, and into the femoral vein at 60 to 80 cubic centimeters per minute. A 5 lead electrocardiogram was connected to the animal and a continuous tracing was obtained from the chest lead V-2.

The equipment used for the perfusion included the afferent and efferent tubing, sigma motor pump, and the resin column, shown in Figure 1. The resin column was fabricated from a pyrex tube, 1 inch in outside diameter and 55 centimeters long. A single hole rubber stopper with glass tubing connected the pump to the column. A small bed of spun glass or tight mesh gauze was placed at the distal end of the column to prevent the resin beads from passing out of the column and plugging the filter. The distal end of the column was attached to a blood filter which led into the venous return polyethylene tubing. The column was placed at a 35 degree slant,

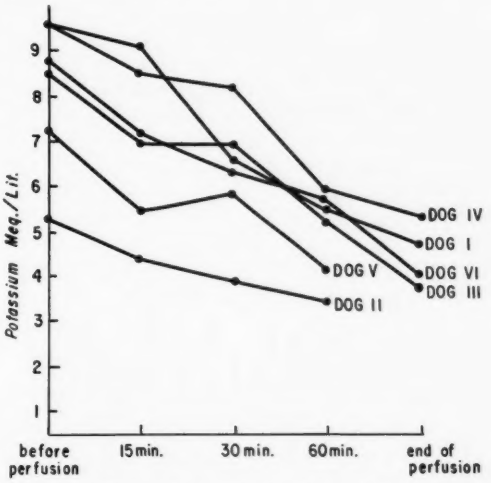


FIG. 3. Changes in serum potassium values in animals perfused 1 to 2 hours.

which allowed more efficient flow of blood through the resin. Aseptic technique was not used, although the resin may be heat sterilized at temperatures up to 150 degrees C. without chemical or physical changes.

The resin used in the laboratory was dowex 50-X8, a sulfonated copolymer of polystyrene and divinylbenzene, mesh size 20 to 50, the structure of which is diagrammed in Figure 2. Before using the resin, it was first washed with water to remove all

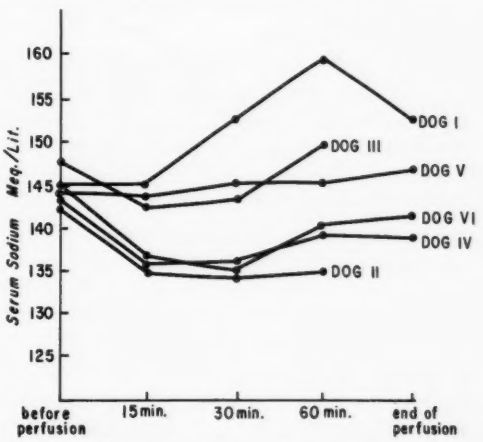


FIG. 4. Changes in serum sodium values in animals perfused 1 to 2 hours.

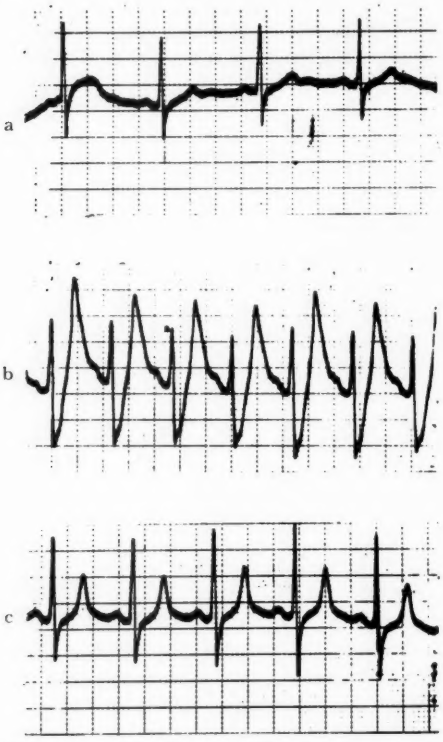


FIG. 5. Case 1. Electrocardiographic patterns paralleling changes in serum potassium. a, On 9 August 1959, serum potassium was 6.2 milliequivalents per liter. b, Resin column perfusion started 12 August at 12:30 a.m. when serum potassium was 9.8 milliequivalents per liter. c, After 6 hours of resin column perfusion, serum potassium was 6.7 milliequivalents per liter.

of the impurities and granules which were of a size smaller than 20 to 50 mesh. The resin was then "re-cycled" to make certain that it was entirely in the sodium form. Hydrochloric acid was added to convert the resin to the acid form. The resin was rewashed and an excess of sodium hydroxide was added to convert all of the resin beads into the sodium cycle. It was then thoroughly washed until the supernatant fluid gave a neutral reaction to hydrazine paper. This procedure assured that the resin was of uniform particle size, neutral *p*H, and that all exchangeable ions were in sodium form.

The resin was then placed in the column in the moist form. Because of the variability of the water content, the weight of the resin varied between 100 and 150 grams. Before starting the perfusion, the circuit was primed with 120 cubic centimeters of heparinized saline. Blood samples were drawn from the jugular vein for serum determinations of calcium, sodium, potassium, chloride, carbon dioxide, and blood urea nitrogen. Blood samples were taken at 15 minute intervals and at the termination of the experiment. Blood was also drawn from the venous side of the resin columns, just before the blood re-entered the dog. These samples were analyzed for sodium, potassium, and calcium.

RESULTS

From 74 to 90 hours after bilateral nephrectomy, the serum potassium was elevated above normal in all animals except one. Serum potassium levels ranged between 5.3 and 9.6, with an average of 8.16 milliequivalents per liter. At the time of perfusion, all animals were moribund with elevated blood urea nitrogens ranging between 32 and 240 milligrams per cent. Table I is a composite tabulation of the changes in serum values of the 6 animals during the course of perfusion. It may be observed from this table and from Figure 3, that, in all animals, the serum potassium decreased after perfusion. Also, there was a small rise in the serum sodium levels (Fig. 4). In all animals, except dog V, there was a minimal drop in blood urea nitrogen. Autopsy was performed on 3 of the animals after perfusion. There was no intra-abdominal bleeding or other gross abnormality. No hemolysis was observed. There was a minimal drop in blood pressure in 3 of the animals, ranging between 10 and 40 millimeters of mercury, which could be controlled with small doses of neosynephrine intravenously.

Table II demonstrates that the blood samples taken from the efferent end of the column showed consistently low serum potassium and calcium values with a serum sodium level that was always elevated

above that of the animal. However, after perfusing dog VI for 120 minutes, the animal's serum potassium and calcium levels were approximately equal to the values of samples drawn from the efferent end of the column.

CLINICAL STUDIES

Three patients with acute hyperkalemia were treated by perfusion of their blood through a resin column. The apparatus used was identical to that described before, except for the resin columns themselves. The columns used in Cases 1 and 2 consisted of a vinylite hemorepellent casing containing 50 grams of dowex 50-X8, sodium cycle.

CASE 1. A 42 year old man was admitted to the University of Oregon Medical School Hospital with charring electrical burns of both hands and arms and a history of prolonged hypotension and anuria. On the second hospital day, the patient's condition suddenly deteriorated. He became comatose and hyperpyrexic, and an electrocardiogram showed changes consistent with marked hyperkalemia. The patient was heparinized, and extracorporeal perfusion through resin columns was begun. Figures 5, 6, and 7 illustrate the changes in electrocardiograms and serum electrolytes during the course of the patient's perfusion.

The change in the patient's condition was dramatic. He became responsive, oriented, and his blood pressure and respirations stabilized. Twelve hours after perfusion, the charred upper extremities were amputated. The dissection was of necessity extensive and prolonged in order to resect all nonviable tissue. During the course of the procedure, the blood pressure could not be maintained in spite of adequate blood replacement and other supportive measures. The patient died shortly after his return to the recovery room.

CASE 2. A 62 year old white male entered the Portland Veterans Administration Hospital on 2 June 1959 with an absent left femoral pulse, pain, and discoloration of the left great toe. On 21 September 1959, an aneurysm involving the distal portion of the aorta and left common iliac artery was resected and replaced with a teflon graft. The patient became anuric, and uremia and hyperkalemia developed, requiring dialysis on the Kolff artificial kidney on 2 occasions. On 5 October 1959 the patient underwent rapid clinical deterioration, his serum potassium became markedly elevated, and there were dissociative hyperkalemic changes on the electrocardiogram. Since there was insufficient time to set up the artificial

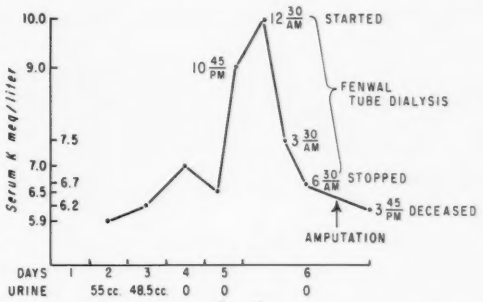
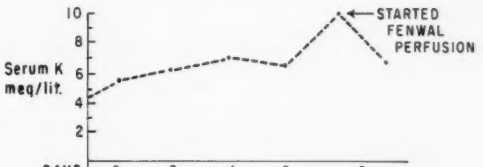


FIG. 6.



DAYS	2	3	4	5	6 2:30 a.m. 6:30 a.m.
Na	144	127	134	122	122
Cl	102		89	89	87
HCO_3			16	20	21
BUN	42		54	150	
Ca^{++}				7.1	
P				10.4	

FIG. 7.

FIG. 6. Case 1. Changes in serum potassium levels throughout clinical course.

FIG. 7. Case 1. Serum electrolyte changes throughout clinical course.

kidney for the third time, his blood was perfused through the resin columns. After perfusion for 4½ hours at flow rates between 300 and 350 cubic centimeters a minute, the patient showed marked clinical and electrocardiographic improvement. Table III shows the changes in the patient's electrolytes during the procedure. The patient subsequently died of staphylococcal pneumonia.

CASE 3. A 28 year old male was admitted to the University of Oregon Medical School Hospital on 25 November 1959, comatose and anuric after a head injury. He had undergone peritoneal dialysis before admission but was comatose, with marked decerebrate rigidity, elevated serum potassium, blood urea nitrogen, and electrocardiographic abnormalities consistent with hyperkalemia. Peritoneal dialysis was repeated with a transient drop in his serum potassium, but subsequently the serum potassium abruptly rose to 8.9 milliequivalents per liter and the electrocardiogram showed even more marked dissociative changes. The patient was immediately heparinized and his blood was perfused through resin columns similar to those used for the experimental procedures, the columns having first been autoclaved. At the end of 2½ hours of perfusion, the electrocardiogram had

TABLE I.—COMPOSITE TABULATION LEVELS OF SERUM ELECTROLYTES IN DOGS UNDERGOING PERFUSION WITH CATION RESIN

Dog	Preperfusion						15 minutes after perfusion		30 minutes after perfusion		60 minutes after perfusion		Postperfusion					
No.	Na^+	K^+	CL^-	NCO_3^-	B.U.N.	Ca^{++}	Na^+	K^+	Na^+	K^+	Na^+	K^+	Na^+	K^+	CL^-	HCO_3^-	B.U.N.	Ca^{++}
I....	145	9.6	70	35	240	8.2	145	9.0	152	6.53	159	5.4	153	4.7	80	30	225	7.05
II...	142	7.3	71	22	235	12.4	135	5.4	134.9	5.9	135	4.2	135	4.2	86	16	220	13.0
III..	147	5.3	107	22	32	10.9	142	4.4	143	3.9	148	3.5	148	3.5	105	18	27	12.2
IV..	143.8	9.6	100	17	215	15.4	136	8.5	136	8.2	139	6.0	138	5.4	93	15	193	11.5
V...	143.6	8.5	109	20	135	13.2	143.6	7.0	145	7.0	142	5.5	145	4.6	100	16	135	11.9
VI..	145	8.7	95	16	200	9.4	137.8	7.2	134	6.9	139	7.2	140	4.4	93	12	190	5.0

TABLE II.—SERUM ELECTROLYTES FROM EFFERENT END OF RESIN COLUMN

	Time after perfusion														
	15 minutes			30 minutes			60 minutes			90 minutes			120 minutes		
Dog No.	Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}
I.....	160.9	0.54	1.04	166	0.47	*	158	2.1	*						
II.....	138.7	0.45	0.9	128	0.41	0.68	137.8	0.41	0.45						
III.....	148.8	0.3	0.6	149.4	0.3	0.35	152	0.8	0.7						
IV.....	147.9	1.3	0.9	139.2	1.0	0.9	142.9	1.0	1.2	140	1.1	1.3			
V.....	150.8	1.3	0.9	150.8	1.15	0.6	149.6	1.75	0.8	147	1.35	0.7	150	1.3	0.6
VI.....	130.5	0.9	0.5	142	1.2	0.8	145	1.3	0.6	147	1.5	0.9	139	4.3	4.7

*These values were not determined on this dog.
Note that in dog VI resin became saturated at 120 minutes.

reverted toward normal; however, a hematoma had formed around the venous cannula, and it was necessary to discontinue the procedure and administer protamine to remedy the clotting defect. Table IV depicts the changes in this patient's electrolytes. He died 48 hours later of irreversible central nervous system damage.

DISCUSSION

From the data, the most consistent and dramatic result is the decrease in the serum potassium in all patients and experimental animals as a result of perfusion. In 2 animals (dogs II and V) there was a transitory rise in the serum potassium before the termination of the perfusion; that is probably the result of laboratory error. All animals showed significant decrease in serum potassium levels between initial and final values. Moreover, the changes in the electrocardiogram, both dog and human, showed marked dissociative changes before, and reversion to normal after the procedure (Figs. 5 and 8). Dog III had a preperfusion serum potassium of 5.3 milliequivalents per liter and a normal electrocardiogram initially, but even this animal showed a consistent drop in serum potassium.

One would anticipate that the serum sodium level should rise during the perfusion as the resin exchanges sodium ions for potassium, calcium, and magnesium ions. The sodium did rise, but not in an entirely consistent manner. Initially, there appeared to be a mild decrease in the serum sodium concentration and then a gradual, small rise. Possible explanations for these findings are: (1) The decrease may be the result of dilution, in that the resin circuit was primed with 150 cubic centimeters of isotonic saline and the animal was given a small amount of fluid intravenously before starting the perfusion. (2) There may have been a shift of sodium into the cell as the serum concentration of potassium dropped, and this may account for the more gentle rise of the sodium curve during the course of the perfusion. (3) In our laboratory, the error for determinations of serum sodium is 3 milliequivalents per liter, whereas for serum potassium the reliability is .3 milliequivalents per liter, so the variation may be within limits of the procedure.

In all animals, except dog V, the blood urea nitrogen dropped. As has been observed by other workers studying resins, this may be the result of the dialysis phenomenon between the resin and the water interface surrounding it.

At flow rates of 60 to 80 cubic centimeters per minute, the resin removed nearly all of

TABLE III.—CHANGES IN ELECTROLYTES DURING PERFUSION WITH RESIN COLUMNS IN CASE 2

	Na^+	K^+*	Ca^{++}	K^+†
Before perfusion	135	7.45		
1 hour	137	6.0		5.45
2½ hours	146	4.8		0.5
3 hours	145	4.1	5.6	0.55

* Serum potassium from patient.
† Serum potassium from distal end of resin column.

TABLE IV.—PERFUSION WITH RESIN COLUMNS IN CASE 3

	Na^+	K^+	Cl^-	HCO_3^-	B.U.N.	Ca^{++}
Before perfusion	141	8.4	98	21	260	6.8
After perfusion	138	7.4	90	18	220	13.2

the potassium and calcium from the blood perfused through the columns. At the end of 1 hour of perfusion, the concentration of calcium and potassium from the efferent side of the resin column was consistently low but after 2 hours (Table II, dog VI) the concentrations were approximately the same, indicating saturation of the resin. Similar results were observed in Case 2. At the end of 1 hour of perfusion, the patient's serum potassium and the potassium from the efferent end of the resin column were approximately equal (Table III).

All patients showed clinical improvement; the changes in the electrocardiograms were dramatic. Although all expired, it was not thought that their deaths were attributable to hyperkalemia or to the perfusion procedure. There were no serious adverse reactions to the use of the resins. The animals exhibited a drop in blood pressure which could be controlled with small concentrations of vasopressors. Perhaps anesthesia, or lack of aseptic technique with resulting bacteremia, may have been partially responsible. Hypotension was not observed in the clinical studies. The only complication encountered in patients was bleeding around the cannula as a result of overheparinization in Case 3. The bleeding was rapidly controlled by administering intravenous protamine.

This procedure has several advantages over previously described methods, including conventional hemodialysis: (1) The method is uncomplicated and inexpensive. (2) It does not require large amounts of blood to prime the perfusion circuit. (3) The time required to assemble and operate this apparatus is short. (4) The procedure does not require a team of highly trained specialists.

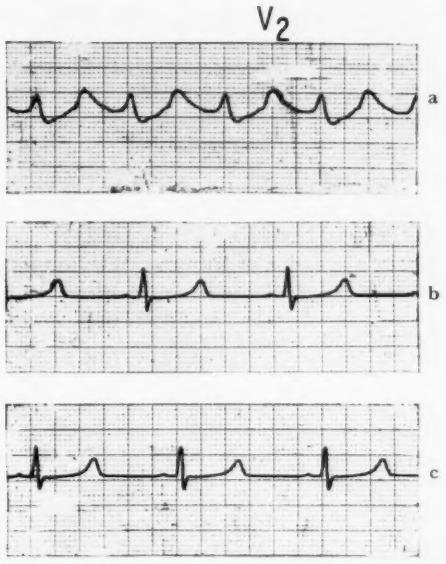


FIG. 8. Dog I. Bilateral nephrectomy. a, Serum potassium was 9.6 milliequivalents per liter 72 hours after operation. b, It was 6.2 milliequivalents per liter 35 minutes after perfusion with cation exchange resin. c, Serum potassium was 4.7 milliequivalents per liter at 90 minutes after perfusion. Note electrocardiogram reverts to normal 35 minutes after perfusion.

Although we experienced few complications, the procedure is not without possible dangers. Because of the efficiency of the resin for removal of potassium, magnesium, and calcium, depletion of these cations may rapidly occur. Calcium and magnesium should be replaced and the patient's clinical course be followed by carefully observing vital signs, by frequent determinations of serum potassium and calcium levels, and by continuously monitoring the electrocardiographic changes.

From the experimental results and from our clinical experience with this method, we believe that resin perfusion may be of definite, practical, and perhaps lifesaving value in certain clinical situations. We have

found it especially useful when there is a rapidly rising serum potassium which cannot be controlled by conservative measures, or if there is insufficient time to carry out the necessary preparation for dialysis with the artificial kidney. Other possible applications are treatment of hypercalcemia and removal of ammonium ions from the blood of patients in hepatic failure.

Resins, because of the versatility of their exchange reactions, because of their ability to act as a dialyser, and because of their adsorptive properties, are compounds which offer possibilities for research in many directions. Kolff has stated that, "The future for a resin artificial kidney is practically unlimited and unexplored." At present we do not know the nature of the toxic substance or substances which produce the clinical syndrome of uremia. It is not beyond the realm of possibility to develop a resin that would selectively remove toxic metabolites from uremic patients, thus identifying the agents responsible.

SUMMARY AND CONCLUSIONS

A method for rapid, safe, and efficient treatment of acute hyperkalemia has been described. This consists of perfusing blood through a cation resin column using an extracorporeal pump circuit. Results are based on animal and clinical studies. In all instances there was a decrease in serum potassium levels. The patients were clinically improved.

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THROMBECTOMY FOR ACUTE ILIOFEMORAL VENOUS THROMBOSIS IN THE POSTPARTUM PERIOD

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ACUTE iliofemoral venous thrombosis occurs classically in the postpartum period when the tensely swollen, constantly aching lower limb is associated with lactation. This is the familiar "milk leg." Although fatal pulmonary embolization is rare the severe pain and swelling are incapacitating. In addition, the troublesome late sequelae of the postphlebitic limb are a serious problem to the young patient, especially for the young mother with many years of footwork ahead of her. The debilitating nature of both the acute and chronic symptoms indicates an urgent need for better therapy.

Immediate removal of the venous thrombus as proposed by Leriche (5) and recently reintroduced by Mahorner has received less clinical trial than seems indicated on the basis of our early results with this method. This article is presented to describe our experience with emergency thrombectomy of the iliofemoral veins in 5 postpartum patients with acute phlegmasia alba dolens.

CASE REPORTS (TABLE 1)

CASE 1. A 37 year old colored female had a full term spontaneous delivery and was discharged on the third postpartum day. One month later, acute thrombophlebitis developed in the right calf with massive edema and the clinical picture of iliofemoral venous occlusion. Bed rest and antibiotics at home gave little relief, and she had severe pain for 10 days. She was ambulated in her fourth week, and 4 days later the same pain and swelling developed in the opposite leg. After 3 days, she was admitted to the hospital with a tensely swollen left lower extremity and slightly cyanotic toes. There was slight residual edema of the right foot but the left leg measured 1 to 2 inches greater in diameter at each level. Under spinal anesthesia the edematous femoral canal was explored, and black gelatinous clots were removed from the femoral and iliac veins with good proximal bleeding but poor distal return despite attempts at flushing from the ankle. The common femoral artery was in marked spasm with a weak pulse. She was given 75 milligrams of heparin intravenously during the procedure. The pain was immediately relieved, and the edema disappeared in 3 days. She was ambulated on the sixth postoperative day with elastic bandage support and maintained on oral dicumarol for 3 weeks. She was seen 17 months later with slight residual swelling of the leg which had not been operated upon but she was without complaints.

CASE 2. A 28 year old colored woman delivered her seventh child spontaneously and had a tubal ligation for grand multiparity. On her fourteenth postpartum day, sudden aching pain developed in the left lower thigh and calf, and her foot became cold. Because of the pain she went to bed but progressive swelling ensued and involved the whole leg by the following morning. Examination revealed a tensely swollen, hot, tender left leg measuring 2 inches greater at the midcalf and midthigh than the right leg. The inguinal area of the femoral canal was exquisitely tender and indurated. She was immediately given anticoagulants and operated upon under local anesthesia 70 hours after onset of leg pain and 60 hours after development of massive edema. The femoral vessels were encased in brawny edema. The vein was thick walled and filled with black thrombus. By pressure and suction, long coagula were extruded with excellent peripheral back bleeding but bleeding from the pelvis was never brisk. There seemed to be a valve present at the hypogastric area, for free bleeding occurred with the glass tip fully inserted to the caval level but did not persist when it was removed. The venotomy was closed with No. 5-0 arterial silk. She was free of aching leg pain immediately and was discharged on oral anticoagulants on the sixth postoperative day. She had slight residual edema of the lower leg on discharge but was fully ambulatory. She was last seen 10 months after thrombectomy. There was no measurable difference in the two legs and she was back at work without complaints.

CASE 3. A 19 year old colored woman had an uncomplicated vaginal delivery under saddle block anesthesia on 29 November 1959 with discharge on the third postpartum day. She remained well until the eleventh postpartum day when her left calf became stiff. This stiffness progressed rapidly to massive edema and inability to stand on the leg on admission.

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TABLE I.—POSTPARTUM PATIENTS WITH IMMEDIATE ILIOFEMORAL THROMBECTOMY

Case No.	*Age, yrs.*	*Delivery*	*Onset of symptoms, days after delivery*	*Time of operation, days after symptoms*	*Operative findings*	*Postoperative course*	*Present condition*
1	37	Vaginal	50*, 76	3	Iliofem. thrombus—fresh. Incomplete removal	Pain relief at once; edema gone 3 days	No edema or pain 17 mos.
2	28	Vaginal—tubal lig.	14	3	Iliofem. thrombus—fresh. Complete removal	Pain relief at once; sl. ankle edema 6 days	No edema or pain 10 mos.
3	19	Vaginal	11	3	Iliofem. thrombus—fresh. Complete removal	Pain relief at once; edema gone 2 days	No edema or pain 11 mos.
4	30	Vaginal	1	2	Iliofem. thrombus—fresh. Complete removal	Pain relief at once; edema gone 5 days	Sl. foot edema; no pain 9 mos.
5	36	Low cervical cesarean	9	2	Iliofem. thrombus—fresh. Complete removal	Pain relief at once; edema gone 6 days	No edema or pain 7 mos.

*Patient had bilateral thrombophlebitis; first episode treated with bedrest and penicillin.

Examination revealed a healthy lactating patient with a healing episiotomy incision. She had an exquisitely tender left femoral canal, a tensely swollen hot leg, a positive Homans' sign, and many dilated superficial veins over the calf and knee. The left leg measured 1 inch in diameter greater than the right leg at all levels. She was given heparin on the ward and operated upon 70 hours after the onset of the painful swelling in the leg. The patient refused operation under local anesthesia because "my leg is too painful to touch," so cyclopropane anesthesia was used. The femoral canal was filled with such edematous tissue that dissection was tedious. The superficial femoral artery had a very weak pulsation and was in marked spasm. The common femoral vein and tributaries were dull white and very thick walled. They were filled with black coagula which were easily extruded by milking pressure. The suction tip was passed into the iliac vein with removal of more thrombus material and very active back bleeding. The venotomy was closed with No. 5-0 silk, and elastic bandages were applied. On awakening from anesthesia she noted that all pain had disappeared from the leg. The edema was gone by 48 hours. Oral administration of anticoagulants was continued, and she was ambulated on the sixth postoperative day. At the time of discharge leg measurements were identical and remained so. She was last seen 11 months after thrombectomy free of complaints and engaged in active housework.

Case 4. A 30 year old white female was delivered vaginally on 31 January 1960. She had had nothing suggestive of pelvic inflammatory disease. The membranes ruptured spontaneously during the 12 hour labor. During the early hours of labor there was some aching in the left thigh with questionable edema of the left foot. Twelve hours after delivery acute iliofemoral thrombosis developed with an exquisitely painful edematous left leg. The operation was delayed for 24 hours because of fear of full heparinization so soon after placental separation. Forty hours from the onset of massive edema, the completely thrombosed iliac and femoral veins were evacuated of black coagula with excellent resumption of blood flow. Xylocaine hydrochloride infiltration anesthesia was very satisfactory. Her pain disappeared immediately, and the edema subsided in 3 or 4 days although she ran a very febrile course with evening temperatures to 104 degrees orally for 5 days and then spontaneous defervescence occurred. No antibiotics were used. She was ambulated on the sixth day and maintained on oral dicumarol for 3 weeks. She is wearing elastic bandages at 9 months because of very slight edema.

Case 5. A 36 year old white female had a low cervical cesarean section on 30 January 1960, after failure of induction of labor for postmaturity. She was discharged with a healthy baby on her seventh postoperative day and noted aching pain in the left calf 2 days later. This progressed in 12 hours to marked edema of the left leg with exquisite tenderness in the left groin area. On the tenth postpartum day she was operated upon under local anesthesia. A large black coagulum extruded itself through the common femoral venotomy. The glass suction tip was inserted to the iliac vein level with removal of more thrombus material and excellent back bleeding. The distal venous return was sluggish until the calf was compressed. Then a venous cast 18 inches long was extruded with very brisk bleeding. Fifty milligrams of heparin were given intravenously, and the venotomy was closed with No. 5-0 silk. All leg pain was gone the following morning. She was ambulated on the sixth postoperative day and discharged 7 days later. At the time of discharge there was no dependent edema and no leg pain. Oral anticoagulants were continued for 3 weeks. At her 7 months follow-up visit the leg appeared normal; she was asymptomatic.

DESCRIPTION OF OPERATIVE TECHNIQUE

Under ½ per cent xylocaine regional anesthesia, an S-shaped incision is made

over the femoral canal beginning about ½ inch below the inguinal crease. The vascular components of the canal are isolated with umbilical tapes around the common, superficial, and deep femoral veins, and the femoral artery (Fig. 1). This dissection is usually in very edematous tissue. The diagnosis is confirmed when the thick walled, dull-white femoral vein is incised longitudinally and the black gelatinous thrombus visualized (Fig. 2). When the presumptive diagnosis is confirmed the patient is immediately given 50 milligrams of intravenous heparin. If the thrombus is quite fresh it may extrude itself as the incision is made but usually removal of the proximal portion of coagulum is accomplished with a combination of forceful abdominal straining by the patient and manual pressure over the lower part of the abdomen by the operator (Fig. 3). If back bleeding is not brisk an angled glass suction tip is inserted as far as it will advance and further coagulum is aspirated (Fig. 4). If bleeding is still sluggish either No. 14 French polyethylene tubing or a urethral catheter is inserted and advanced to the level of the inferior vena cava. Attention is then directed distally where manual compression of the calf and thigh with a gentle milking motion usually dislodges large quantities of black thrombus. Again, if bleeding is not active, the suction tips are used until the venous return is brisk. The venotomy is irrigated with diluted heparin solution and closed with continuous No. 5-0 arterial silk. The wound is then closed in layers without drainage, and elastic bandages are applied from the foot to the groin.

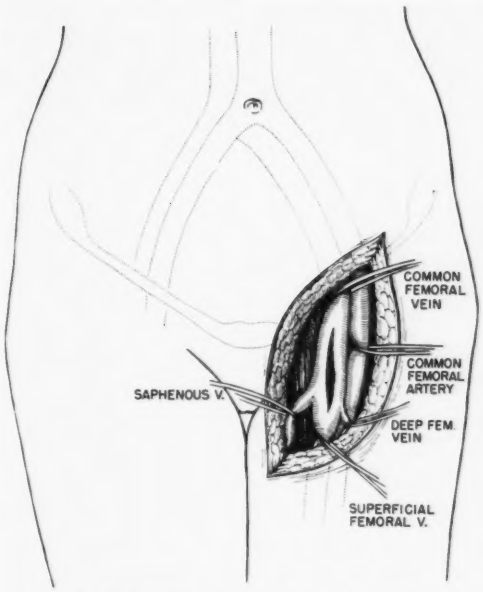

FIG. 1. Anatomic exposure for iliofemoral venous thrombectomy. The longitudinal venotomy reveals the black thrombus.

USE OF VENOGRAPHY

Venograms were carried out before and after thrombectomy in all the early cases and are still used in certain selected cases. When venography is used, a cutdown is made below the lateral malleolus and one of the veins cannulated. A venous tourniquet is placed above the ankle and 40 to 50 cubic centimeters of 50 per cent hypaque are rapidly injected. Full length leg films are exposed 4 to 5 seconds after the last cubic centimeter of dye is injected. This is essentially the technique used by DeWeese and Rogoff. The venogram is usually repeated after the thrombectomy. The venograms obtained in Case 2 before and after thrombectomy are shown in Figure 5.

Venography is not necessary in the usual case. It was used to supplement the clinical diagnosis early in this experience and to verify early results of thrombectomy. In the atypical case it may demonstrate the deep vein thrombosis and it may be very useful as a baseline control in the subsequent follow-up of these patients to determine the status of the deep venous system.

DISCUSSION

A consideration of the etiology of iliofemoral thrombosis in the postpartum patient is a particularly intriguing one, for most of the theoretic factors in intravascular clotting are present. Stasis will not be denied

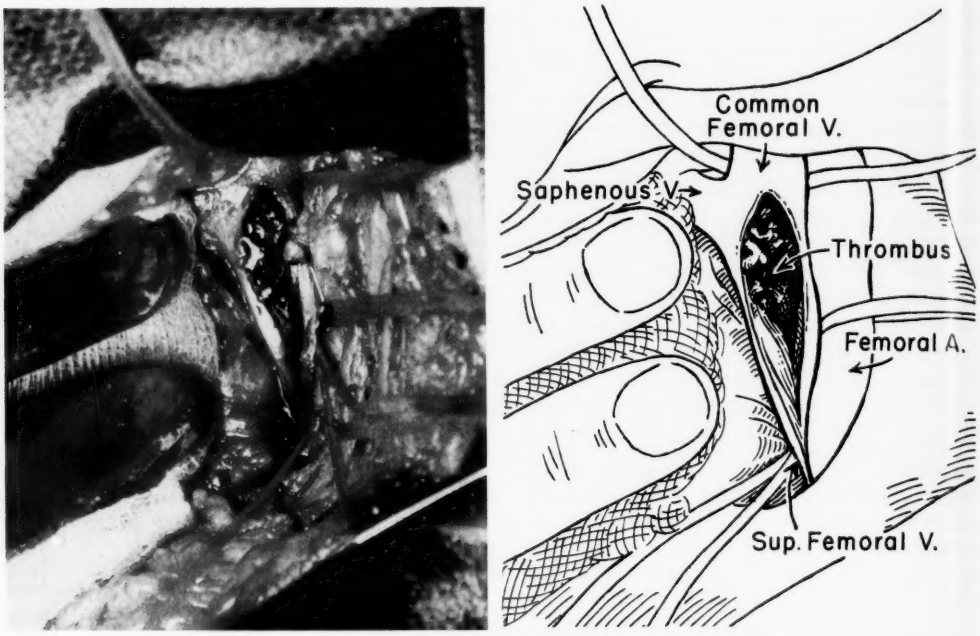

FIG. 2. Operative photograph showing thrombus material in femoral vein.

by any woman who has gone through the latter months of pregnancy and especially the first and second stages of labor. Dependent edema and enlargement of existing varices visibly document the presence of venous obstruction. The development of thrombosis seldom occurs during this period, however; but rather, it is found in the postpartum period some time after the relief of this physiologic obstruction. Infection may occasionally play a role in thrombosis, especially if it is associated with premature rupture of the membranes, but it is difficult to relate this localized uterine contamination to infection along the iliac vessels unless there is a far advanced puerperal fever with septic pelvic phlebitis. Massive thrombosis and fatal septic emboli may accompany this rare condition but the sepsis far overshadows the thrombosis. The pathogenesis of septic pelvic thrombophlebitis indicates that pelvic vein thrombosis may be propagated into the iliac and femoral veins. It was noted by Collins and his associates that the best results in therapy of septic pelvic thrombophlebitis have been achieved by proximal vein ligation—usually the common iliac or inferior vena cava.

The effect of the obvious trauma which must be incident to the passage of the infant's head along the pelvic floor cannot be excluded as a factor in subsequent thrombosis. But again, most of the effect of this direct trauma has subsided at the time when thrombosis usually occurs in the third to tenth postpartum days. Nevertheless, this direct trauma to the veins and the stasis and immobility associated with labor and the puerperal period would seem a logical combination of factors to explain the occurrence of phlegmasia alba dolens. This concept was very satisfactory indeed, until acute thrombosis developed in the patient with an elective cesarean section (Table I). Her membranes were intact; she had no prior ankle edema and was not in labor.

Figure 6 is a modified diagram (4) which calls attention to what should have been

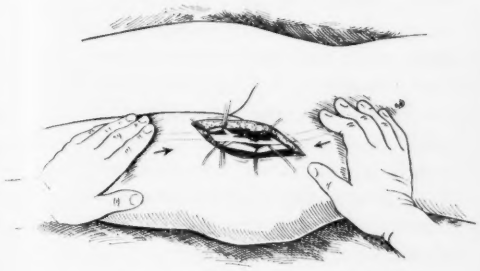

FIG. 3.

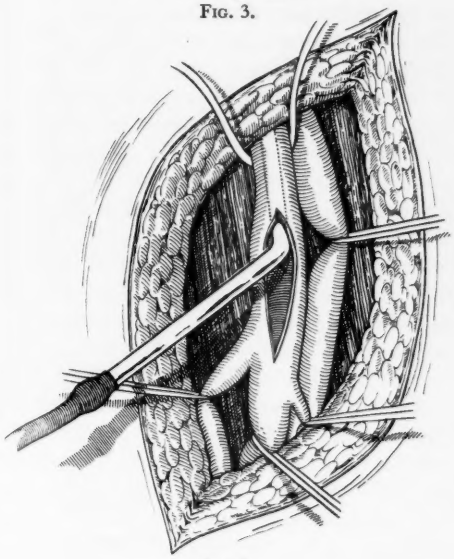

FIG. 4.

a b

FIG. 5.

FIG. 3. Manual pressure on lower part of abdomen and thigh used to extrude soft coagulum from iliofemoral veins. Patient has been heparinized prior to this procedure.

FIG. 4. Glass aspirator inserted into iliac vein to remove tenacious thrombus material.

FIG. 5. a, Prethrombectomy venogram obtained in Case 2 showing failure of filling of deep venous system and major saphenous veins. Note many fine superficial venules in upper and lower leg. b, Postthrombectomy venogram in same patient documenting patency of deep veins and portions of the saphenous system. Note the many valves which appear to function normally.

an obvious and possibly an important additional factor. Physiologic venous thrombosis accompanies every delivery, for the placental site must thrombose. Often there is some proximal extension into the uterine veins. Even without sepsis it seems possible that this might involve the hypogastric drainage and by extension, just as in pelvic thrombophlebitis, also involve the iliac veins. One additional factor may contribute to this tendency to propagation and that is the postpartum diuresis and consequent hemoconcentration which slows blood flow at about the onset of lactation. The term "milk leg" certainly connotes the common occurrence of this condition at the time of lactation and may be another example of popular observance of a pathophysiologic entity.

The acute symptoms of intense pain and massive edema respond only slowly to the time-honored therapy of bed rest, elevation, anticoagulants, and narcotics and to the more recently advocated epidural block.

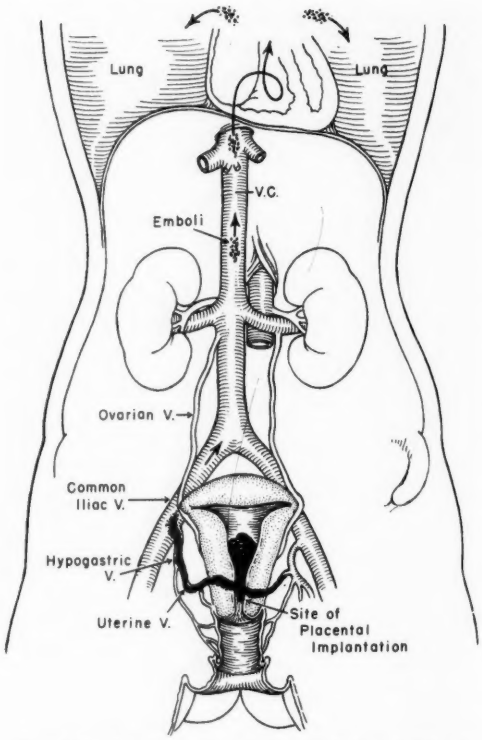

FIG. 6. Possible route of propagation of thrombus from placental site in postpartum iliofemoral venous thrombosis. Note extension into hypogastric and into iliac veins. Modified from Eastman, N. J., *Williams Obstetrics*, 11th ed., p. 982. New York: Appleton-Century-Crofts, Inc., 1956.

Fearful though it appears this distressing condition is not often complicated by pulmonary embolization, for apparently, the accompanying inflammatory reaction fixes the thrombus to its origin. Systemic anticoagulation directed toward prevention of further propagation of the thrombus is obviously important and has been recently emphasized by Anlyan and his associates. However, it does not return the veins and their valves to normal function, so it cannot be expected to prevent the postphlebitic limb.

None of the components of presently accepted therapy attempts to prevent the lasting result of the disease, namely, destruction of the directional flow of the deep venous system of the leg. This is a far more serious consequence of massive venous thrombosis than has been formerly emphasized. The thrombosed iliac and femoral veins eventually become recanalized but their valves are incompetent. Left with valveless veins the majority of patients become victims of a chronically edematous, aching, ulcer prone extremity. These sequelae of massive thrombosis often elude a causal relationship to the initiating venous occlusion because the after effects may occur long after the initial recovery.

It was to relieve this second and possibly more important complication of iliofemoral thrombosis that Fontaine in 1950 and Mahorner in 1952 began removing the thrombus material. In 1957, Fontaine reported 26 cases with a 2 to 6 year follow-up and good or excellent results in 20 of them. The following year Mahorner published his results in 16 patients with gratifying results in 14 but with a much shorter follow-up period. Several of Mahorner's patients had long standing thrombosis (4 and 6 months) in which restitution of valve function could hardly be expected. In only 1 case did thrombosis occur in the postpartum period. The eventual operation was not carried out until 8 months later. The failure of thrombectomy in this patient is not surprising. As far as can be ascertained, there have been no reported cases of successful thrombectomies in postpartum women, probably because these patients are not often under direct surgical supervision.

The follow-up has not been long enough to establish with certainty whether early thrombectomy restores function to the deep veins. But it can be shown that the valves are intact and functioning as demonstrated clinically by the subsidence of edema and roentgenologically by preoperative and postoperative phlebography. If the valves remain free the results should remain good.

Another of the less dramatic but equally satisfying effects of thrombectomy is the immediate relief of all pain. This is usually quite striking and much appreciated by the

seriously incapacitated young mother. She can nurse her baby in comfort and take over its full time care in a matter of a few days.

ANTICOAGULANTS

The superiority of heparin over other drugs in preventing the extension of thrombosis is fairly well established but the outpatient control of this drug regimen is still unreliable. The empiric time of 3 weeks of anticoagulation is used because all evidence of inflammation is gone by then (usually by 1 week) and full ambulation is in effect. Because of the control problem, dicumarol is used for out-patient therapy with weekly determinations of prothrombin times.

THROMBOLYTIC AGENTS

The very active research in the use of fibrinolytic substances and some encouraging experimental results with these materials may soon make available another means of thrombectomy. It seems doubtful that these substances will supplant direct removal of the huge iliofemoral thrombus, but they may be very useful in dissolving retained clot in the many smaller collateral channels.

CONCLUSION

Phlegmasia alba dolens constitutes a serious complication of pregnancy which is occasionally fatal from pulmonary embolization but is much more often debilitating through the development of a postphlebitic limb. Older methods of anticoagulation alone or vein ligation can be expected to prevent embolization, but immediate thrombectomy is the only available means of reconstituting function in the thrombosed iliofemoral veins. Whether the thrombolytic agents will eventually be safe and effective in the removal of this clot is presently not known. Until these agents have been more widely proved every patient with acute iliofemoral thrombosis should have an immediate thrombectomy with full anticoagulation during the course of and after the procedure.

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CLINICALLY "BENIGN" GASTRIC ULCERATIONS FOUND TO BE MALIGNANT AT OPERATION

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FURTHER INVESTIGATION of any method of treatment is worth while when current methods of management seem to have reached a plateau. Earlier operation, changes in the resectability and operative mortality rates, and many preoperative and postoperative aids have been important factors which have led to an increase in the number of patients who have actually survived from carcinoma of the stomach. The 5 year survival rate has reached a plateau of 10 to 15 per cent for all such patients seen and about 30 to 35 per cent for those undergoing curative resection. A review of the clinical aids in diagnosis and the management of patients who have chronic gastric ulcerations is presented. Some of these patients harbor occult carcinoma of the stomach. It appears likely that earlier surgical treatment will improve their chances for survival. These patients comprise an important segment of those who are listed as survivors from carcinoma of the stomach.

The exact incidence of malignant change associated with gastric ulcerations has been disputed for many years but various estimates fall between 5 and 20 per cent.

The symptoms, age, and sex do not differentiate a patient having a benign gastric ulcer from one harboring a malignant lesion. The duration of symptoms as well as so-called temporary healing may cloud the issue and may delay the true diagnosis of malignant disease.

Although roentgenologic diagnosis is usually helpful, the literature contains many reports indicating that it is not as accurate as desired. Ravdin and Horn have pointed out that an ulcer niche can be filled with proliferating carcinoma and yet the roentgenograms show that healing has occurred.

The site and size of the gastric ulceration in question vary so much that they can serve only as rough clinical indexes of the possibility of malignant disease. An associated duodenal ulcer, once thought to be "insurance" against malignant development in a gastric ulceration, is no longer regarded as such.

Walters and Berkson have shown that the 5 year survival rate for patients with carcinoma of the stomach increases from 18.6 per cent for patients with metastasis to lymph nodes to 48.5 per cent for those without. Rhoads expressed the opinion that the over-all currently improved, curative resection rate of about 35 per cent is chiefly the result of earlier diagnosis and recent emphasis on restricting periods of medical management of supposed benign gastric ulcers. Blalock and Ochsner found that nearly 70 per cent of their 5 year survivors who had undergone curative resections for carcinoma of the stomach came from the group of patients who had had gastric ulcerations.

MATERIALS AND METHODS

The files of the Mayo Clinic for the 10 year period 1944 through 1953 were examined for records of all patients who had malignant gastric lesions which had been diagnosed clinically as benign gastric ulceration but who were operated on when first seen because of the severity of their supposed benign gastric ulceration or who were oper-

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Abridgment of thesis submitted by Dr. Brown to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

ated on after 2 weeks or more of medical management. None of the patients had received cortisone, salicylates, or other medications that might have caused acute gastric ulceration. All patients were found to have carcinoma of the stomach at operation.

The records of 106 patients seen during this 10 year period were found to meet the aforementioned criteria. This, obviously, represents a highly selected group of patients with evidence of gastric ulceration. During the same period 1,650 patients with benign gastric ulcers and 1,610 patients with gastric carcinoma had been treated surgically.

CLINICAL FEATURES

There were four times as many men as women in the present study and the predominant ages in both sexes were 40 through 60 years. The physical findings rarely revealed more than vague tenderness in the epigastrium, and the so-called ulcer regime diet, heavy with milk and cream, often provided a good nutritional state.

About 73 per cent of the patients had a typical history of peptic ulceration. Of the other 27 per cent, 14 per cent had symptoms only suggestive of an ulcer pattern and 13 per cent had symptoms that were not consistent with such a pattern. However, 9 patients who had a history of prior cholecystectomy or closure of perforation of peptic ulcer were included in the 27 per cent.

Epigastric pain occurred in more than 90 per cent of the patients. The absence of epigastric pain was an ominous sign, since most patients who did not experience such pain proved at operation to harbor extensive and incurable disease. Pain at night, especially if it extended to the shoulder, the right upper quadrant, or the back, also often indicated a poor prognosis. None of the symptoms were specific in any way for carcinoma. Fifty-eight of the 106 patients mentioned an abrupt change in symptoms within 4 months preceding their operation. In 9 patients, 4 of whom had cholecystectomy, 4 of whom had closure of a perforated duodenal ulcer, and 1 of whom had closure of a perforated gastric ulcer, symptoms suggestive of gallbladder disease or peptic ulceration persisted.

TABLE I.—ACCURACY OF THE VARIOUS MODALITIES OF DIAGNOSIS

Diagnosis (106 patients)	*Patients* — *No.*	*Per cent of total*
Roentgenographic report: Suggested malignant lesion	31	29.2
Internist's report: Possible malignant lesion	18	17.0
Surgeon's report: Recognized grossly as malignant lesion	61	57.5
Uncertain	19	17.9
Benign lesion	26	24.5

DIAGNOSTIC AIDS

Gastric analysis was performed in 101 of the 106 patients, and of the 21 patients in whom the acids were low or absent only about a third survived 5 or more years after operation.

Gastroscopic examination was performed 26 times on 19 patients. In 5 patients significant delay in performing laparotomy could be attributed, at least in part, to an incorrect gastroscopic report. Four of the 5 did not survive 5 years after operation. In the survival group the value of gastroscopy must have been seriously questioned because in the 2 cases in which the lesion was correctly diagnosed as malignant the diagnoses apparently were ignored and the patients were placed on a trial of medical management. Endoscopists at the Mayo Clinic are currently of the opinion that gastroscopy is of limited value as a diagnostic aid in the differential diagnosis between benign and malignant ulcerations.

The decision for surgical intervention was reached, with few exceptions, through the joint efforts of internist, gastroenterologist, and surgeon. In this study, most patients who had a gastric ulceration had been seen in consultation by a surgeon whether operation was advised or not. After a careful review of the clinical picture, laboratory data, and roentgenographic reports on the use of barium and contrast media, the patient was advised regarding treatment.

TABLE II.—INDICATIONS FOR OPERATION

Internist's preoperative diagnosis	*Patients*		
		No.	*Per cent*
Malignancy suggested or suspected (after medical management)		18	17.0
Nonmalignant condition suspected		79	74.5
Intractability or complications	17		
Failure of medical management			
At clinic	24		
Elsewhere	38		
No definite opinion		9	8.5
Total		106	100.0

In tabulating the preoperative diagnoses of the internists it was often difficult to determine whether a patient should be included in the group having a suspected malignant lesion or in the group having a benign lesion. However, if the internist's conclusions gave the slightest suggestion of malignant disease, the patient was included in the former group.

It must be emphasized that the internist recognized that at least 10 per cent of all gastric ulcerations were potentially malignant; however, he was unable to predetermine accurately this 10 per cent from the other benign lesions. Obviously herein lies the problem of the internist.

With all this in mind, a comparison was made of the three modalities of diagnosis including roentgenographic reports, the internist's opinion based on the clinical picture and roentgenographic reports, and the surgeon's opinion based on initial findings at operation (Table I).

Although the surgeon mentioned gross malignancy in his operative report in 61 cases, it was by no means always possible to be certain that his opinion was not biased by the immediate report on frozen sections which were routinely available before the operation was completed. In 26 instances, however, he made a clear-cut declaration of supposed benignancy.

The internist's opinion was correct for malignancy in less than a fifth of the cases and in these only after a period of medical management, occasionally followed by a delay, for months or even years, in the time of operation. In 31 patients none of the three forms of diagnosis were correct for malignancy. In these cases the report of malignancy rested solely with the pathologist.

False healing, as determined by serial or repeated roentgenograms, occurred in 14 patients studied during their medical management either at home or at the clinic. Six of these patients failed to survive 5 years.

Table II shows the indications for operation. Failure of medical management to heal the ulceration led to operation in 80 of the 106 patients. Malignancy, when suspected at all, was suspected only after a variable period of medical management.

These data strongly suggest that attempts to delineate the nature of these lesions by means other than microscopic examinations leave much to be desired insofar as accuracy of diagnosis is concerned.

RESULTS OF TREATMENT

Three hospitals deaths followed operation, 2.8 per cent. All 3 patients had had medical management. One patient died on the seventeenth day after resection of the cardia and end-to-side esophagogastrostomy for a large 7 by 7 by 2 centimeter ulcerating carcinoma near the esophagus. The second patient died of pneumonia and bleeding on the eleventh day after an 80 to 85 per cent Polya (Hofmeister) gastric resection for an ulcerating carcinoma 8 by 7 by 1 centimeter in size. The third patient died after a period of persistent postoperative hypotension and shock 3 days after biopsy of the stomach only.

Two patients were untraced. One had a type A grade 3 adenocarcinoma by the Dukes' classification and was treated with a subtotal (two thirds) gastric resection. This patient was lost to follow-up after 2 years. The other patient had a type B grade 2 adenocarcinoma by Dukes' classification and was treated with a subtotal (three fourths) gastric resection.

As to the types of operation, 92 patients had curative resections: Billroth I, 32 pa-

TABLE III.—FIVE YEAR SURVIVAL RATES FOR EARLY AND DELAYED OPERATION

	Early operation				*Delayed operation*			
	Patients		*Lived 5 or more years after operation*		*Patients*		*Lived 5 or more years after operation*	
Operation	*Total*	*Traced*	*No.*	*Per cent**	*Total*	*Traced*	*No.*	*Per cent**
Curative resection	13	13	12	92.3	77	75	45	60.0
Less than curative	3	3	0	—	10	10	1	10.0
Total	16	16	12	75.0	87	85	46	54.1

*Based on traced patients. Last inquiry, 1 January 1959. Three hospital deaths excluded in the calculation of survival rates.

tients; Billroth II, 55 patients; and total gastrectomy, 5 patients; and 14 had less than curative procedures: biopsies only, 13 patients; and wedge excision, 1 patient. The resectability rate in the 106 patients was therefore 86.8 per cent. Of the 101 traced patients who survived operation, 85 had a history of prior medical management and 69 of these had undergone treatment for more than 3 months. Thirty of the 69 failed to survive for 5 years. One cannot suggest that all 69 harbored a malignant process for the entire duration of their symptoms, but it is not unreasonable to suspect that in some cases concurrent extension to a point of incurability may have attended the delay in surgical treatment. The 5 year survival rate for those patients who had delayed operation because of medical treatment was 54.1 per cent.

Twelve, 75 per cent, of the 16 patients who had immediate operation lived 5 or more years (Table III). When only those patients who had resectable lesions were studied, the following information became apparent: for the 13 patients who had early resection, 12, 92.3 per cent, survived 5 or more years, whereas for the 75 patients having delayed resection, due to medical management, who were traced, 45, 60 per cent, survived for a similar period. It is realized that the groups are small and it is perhaps difficult to form a comparison. However, the evidence is at least suggestive of better results in the group of patients who had earlier resection.

Twenty-one of the lesions were limited to the mucosa and were classified grossly as superficial spreading carcinomas. Where there was greater extension, the primary lesions varied greatly in size—a few measured 6 by 6 by 15 centimeters, but most were about 4 by 4 by 1 centimeter. All patients had ulceration which, in the majority of cases, appeared typically "peptic" with central or eccentric ulcerated portions. Evidence of associated duodenal ulcer was present in 36 patients of whom 22 survived at least 5 years. Multiple ulcerations, one or two of which were rimmed with malignant cells, were found in approximately 10 per cent of specimens. All but three of the gastric lesions were found primarily on the lesser curvature.

Table IV shows the grading of the lesions according to the degrees of cellular anaplasia after the method of Broders. It is of interest that the 5 year survival rate for the 38 patients having grade 4 lesions was 50 per cent. This is particularly significant since the higher grade lesions usually indicate a poor prognosis.

The specimens were further classified as to the degree of extension of the malignancy by a modification of the method of Dukes (Table V).

Carcinoma was limited to the mucosa (similar to Dukes' type A) in 21 specimens. In 50 specimens there was extension through the muscular coat or to contiguous lymph nodes, similar to Dukes' type B. In 32 type C lesions by Dukes' classification the spread was to nodes and distant organs.

It is impressive to note that as a group, the patients in the present series have a much better prognosis than patients with clinically evident carcinoma of the stomach. There was a 5 year survival rate of 90 per cent for patients having type A lesions and of 67 per cent for patients having type B lesions. When Dukes' and Broders' classifications were combined and applied to the

TABLE IV.—FIVE YEAR SURVIVAL RATES ACCORDING TO GRADE OF LESION

Grade (Broders' method)	*Total*	*Patients traced*	*Lived 5 or more —years after operation— No.*	*Per cent**
1	1	1	1	100.0
2	26	25	20	80.0
3	30	29	13	44.8
4	38	38	19	50.0
Lymphosarcoma	8	8	5	62.5
Total	103	101	58	57.4

*Based on traced patients. Last inquiry, 1 January 1959. Three hospital deaths excluded in calculation of survival rates.

TABLE V.—FIVE YEAR SURVIVAL RATES ACCORDING TO DUKES' CLASSIFICATION

Dukes' classification	*Total*	*Patients traced*	*Lived 5 or more —years after operation— No.*	*Per cent**
A	21	20	18	90.0
B	50	49	33	67.3
C	32	32	7	21.9
Total	103	101	58	57.4

*Based on traced patients. Last inquiry, 1 January 1959. Three hospital deaths excluded in calculation of survival rates.

specimens in this series, the factor of extension by Dukes' classification influenced prognosis considerably more than did the type of cell. This is in agreement with the earlier findings of Dochat and Gray in their study of carcinoma of the stomach.

Table VI indicates the size of the ulceration in 89 patients in whom an accurate description was given of the fresh specimen at the time of frozen section.

Of the 60 patients who had carcinomatous ulcerations less than 3 centimeters in diameter, 71 per cent of the traced patients survived at least 5 years. Even in the 29 patients with larger ulcerations the 5 year survival rate was 48 per cent.

The number of patients seen, 56, and the number who underwent resection, 50, in the second 5 year period were only slightly larger than the numbers in the first 5 years, 50 and 42, respectively. Thus the resectability rate was only 5 per cent higher in the second 5 year period.

It is of interest that 50 and 56 patients, respectively, were included in the two 5 year periods, which would cast some doubt as to whether the actual incidence of missed diagnoses of malignant lesions in patients with gastric ulcerations is decreasing. Actually, a few more patients were operated on in the second 5 year period. Also of interest is the fact that the incidence of extramucosal extension has increased from 78 per cent in the first 5 year group, 1944 to 1948, to 82 per cent in the second 5 year group, 1949 to 1955.

Perhaps these differences in percentages are not significant except to underscore the fact that some improvement could have been made by getting the patients to operation earlier.

Therefore, the near plateaus of resectability rate, incidence of extension, and incidence of patients with malignancy in gastric ulcerations thought to be benign suggest that a closer evaluation of the problem of so-called benign gastric ulcerations is indicated.

COMMENT

There is, of course, the question of whether the ulceration is a punched-out area, perhaps due to infarction and necrosis involving the surface of an already existing cancer, or whether the cancer has started as a superficial change about the margins of an already existing benign gastric ulcer. Microscopically, the presence of a centrally or eccentrically placed zone of peptic digestion may suggest an ulcer-cancer sequence. It is oftentimes difficult to prove that hydrochloric acid and pepsin have not produced a peptic ulcer in a patch of malignant gastric mucosa.

On the other hand, the presence of a malignant gastric ulceration in a patient who had undergone 5 years of medical management for an intermittently appearing "ulcer," always in the same spot roentgenographically, suggests strongly an ulcer-cancer sequence in certain instances.

It is a fact that some of the small ulcerations found in the stomach by our usual diagnostic methods may be malignant. Currently, a test period of not longer than 2 weeks of medical therapy for such lesions is recommended by some authors. For various reasons, however, a certain number of pa-

tients slip through these arbitrary time barriers. Eight of 10 patients in this study had had prior medical management and in 50 per cent of them the period had lasted more than 6 months.

In any condition for which operative treatment is proposed, the factor of mortality due to operation must be considered. In this series it was 2.8 per cent. There was no operative death in the group of patients who had immediate operation. It has been pointed out by Marshall that the mortality rate for gastric carcinoma among patients treated medically is 100 per cent.

Postoperative morbidity was rarely a serious problem in our series of patients. Many factors may be considered in reaching a decision for or against surgical treatment of a patient who has gastric ulceration, but we do not consider postoperative morbidity to be a factor important enough to influence the decision for or against surgical treatment of gastric ulcerations if there is the slightest question of malignancy. Cain and associates found that 80 per cent of their patients who had had medical treatment for gastric ulcerations had continued to have symptoms and 38 per cent of this group eventually required operation.

If there is any aspect whatsoever in the history, current physical status, roentgenologic evaluation, location of the ulceration, or response to a short period of management that is suggestive of neoplasm, or if there is a suggestion of reactivation or persistence of a previous ulceration and if the patient is in otherwise good health, operation is advised.

It is generally agreed among gastroenterologists at the Mayo Clinic that patients with gastric ulcers should be hospitalized for a clearly defined period of intensive medical treatment, currently 2 weeks, if operation is not advised when the diagnosis is made. If, at the end of the treatment, roentgenographic evidence of improvement is absent and if the patient's general condition otherwise permits, operation is strongly recommended. If, however, there has been a 50 to 75 per cent reduction in the size of the ulcer roentgenographically, and if the patient's symptoms have regressed, the medical treatment is continued with express instructions for roentgenograms of the stomach to be made after 3 weeks and 6 weeks, then every 3 months for 1 year, every 6 months for a year, and every 12 months thereafter to ascertain, beyond all doubt, that healing has persisted. In a sense these patients might be classified as having a 3 year cure for benign gastric ulceration. It must be brought out that many patients will not follow such an arduous program. Furthermore, the expense involved and the ever-present possibility that the lesion will escape from adequate control with the concurrent risk of associated malignancy in the gastric ulceration are two problems that constantly plague the physician who has outlined such a course of treatment.

TABLE VI.—RELATION OF SIZE OF ULCER TO SURVIVAL FOR 5 OR MORE YEARS

	Number of patients		*Lived 5 or more years after operation*	
Size of ulcer	*Total*	*Traced*	*No.*	*Per cent**
1 cm.....	9	9	8	88.9
1 to 2.9 cm...	51	49	33	67.3
3 to 5.9 cm...	23	23	10	43.5
6 cm. or more	6	6	4	66.7
Size not stated	14	14	3	21.4
Total.....	103	101	58	57.4

*Based on traced patients. Last inquiry, 1 January 1959. Three hospital deaths excluded in calculation of survival rates.

SUMMARY

A group of 106 consecutive patients, who were seen over a 10 year period and who were given a clinical diagnosis of benign gastric ulceration which later proved at operation to be a malignant lesion, were reviewed.

About 85 per cent of the 100 patients gave histories of medical management prior to operation. The resectability rate in the entire series was 86.8 per cent.

Malignancy in gastric ulceration was considered a strong possibility and prompted operation in 17 per cent of the patients but only after a period of medical management. The other patients were operated on because of failure of medical management in

58 per cent or because of symptoms of intractability in 16 per cent.

Patients who had delayed operation and who survived resection had a 5 year survival rate of 60 per cent, whereas patients in the early operation category who survived resection had a 5 year survival rate of 92 per cent. It must be re-emphasized that this is a selected series of patients. The over-all 5 year survival rate for the entire series was 57.4 per cent.

Eighty per cent of the patients with grade 2 lesions by Broders' method and 90 per cent of those with type A lesions by Dukes' classification lived 5 or more years after operation. Seventy-one per cent of patients whose ulcerating lesions measured less than 3 centimeters in diameter survived 5 or more years.

Many patients with gastric cancer who survive for long terms after operation are patients who have had clinically benign gastric ulcerations that proved to be malignant at the time of operation.

Early operation in the treatment of most patients with gastric ulcers that have failed to respond to a short predesignated period of medical management, 2 weeks, should result in a greater number of survivors. This greater number of survivors will aid materially in improving the results in the operative treatment of carcinomas of the stomach.

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SURGICAL ASPECTS OF HYPERSPLENISM IN LYMPHOMA AND LEUKEMIA

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WHILE THE ROLE OF SPLENECTOMY in primary hypersplenism is well defined, its role in the treatment of hypersplenism secondary to malignant lymphomas and leukemias is less clear. Mayo reported 54 cases of splenectomy in chronic myelogenous leukemia, lymphosarcoma, and Hodgkin's disease, and believed that worthwhile palliation was obtained in a number of instances. The operative mortality in his series was less than 5 per cent. Zollinger reported a series of 54 splenectomies performed for secondary hypersplenism. While the outcome in many of these patients was favorable, the results did not approach those obtained in primary hypersplenism. This group included 19 cases of leukemia and Hodgkin's disease. Cole was less favorably impressed by the results obtained in this group of patients. His rather poor results led him to believe that Hodgkin's disease, agnogenic myeloid metaplasia, polycythemia, and leukemia were diseases in which splenectomy was probably contraindicated. Sedgwick and Hume recently reported on a series of 11 patients with chronic leukemia and lymphoma in whom splenectomy was performed for secondary hypersplenism. Eight of their patients were dead within 1 year, and they concluded that splenectomy earlier in the disease would probably offer greater benefit.

This report deals with 36 patients with lymphosarcoma, leukemia, Hodgkin's disease, and agnogenic myeloid metaplasia in whom splenectomy was performed for secondary hypersplenism or symptomatic splenic tumor. The surgical treatment was performed during the past 4½ years so that the final outcome in more recent patients cannot be evaluated. Nevertheless, the encouraging results obtained in a significant number of patients thus far suggests that splenectomy is helpful in managing this group of diseases.

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SELECTION OF CASES

The majority of patients had advanced disease. Duration of disease prior to splenectomy is shown in Figure 1. The average duration for patients with Hodgkin's disease, chronic myelogenous leukemia, and lymphosarcoma was relatively long, when compared to the usual course of these diseases as reported by Wintrobe. This may be the result of successful previous drug and radiation therapy received by the majority of patients or because a more favorable group was selected for operation. The youngest patient was 16 years old, while the oldest was 72 years; the average age was 48 years. The majority of patients had had previous treatment with alkylating agents, radiation, cortisone, or combinations of these. Splenectomy was considered after conservative measures failed to control the hypersplenism. In a number of instances, chemotherapy or radiation had been discontinued because of bone marrow depression resulting from treatment, hypersplenism, or a combination of these factors. When hypersplenism was corrected by splenectomy, further therapy could be instituted in most patients.

In 2 patients, the markedly enlarged spleen produced abdominal pain or pressure, constituting an independent indication for splenectomy, and its removal resulted in

TABLE I.—COMPLICATIONS AND DEATHS FOLLOWING 36 SPLENECTOMIES FOR LYMPHOMA AND LEUKEMIA

Disease	*Complications*	*No.*	*Operative deaths*
Lymphosarcoma	Pneumonia	1	0
	Thrombophlebitis	1	
Chronic myelogenous leukemia	Portal vein thrombosis, subphrenic abscess	1	0
	Postop. hemorrhage and shock	1	1
Chronic lymphocytic leukemia	Postop. hemorrhage and shock		1
Hodgkin's disease	Pneumonia	1	
	Postop. hemorrhage.		1
	Wound infection	1	
Myeloid metaplasia	Postop. hemorrhage and shock	1	
Total		7	3
Per cent complications and mortality		19.4	8.3

alleviation of symptoms. Hypersplenism, associated with depression of one or more blood elements, was the commonest indication for splenectomy. The many factors contributing to the "hypersplenic state" and involved in the decision to carry out splenectomy will be discussed in a separate publication.

PREOPERATIVE MANAGEMENT

Close co-operation between internist and surgeon in the management of these patients was essential. Peripheral blood counts, bone marrow studies, estimation of red cell survival, and splenic erythrocyte sequestration by the radiochromium method described by Jandl and associates were the laboratory aids used in evaluating the hypersplenic state. Splenic aspiration was performed and radioactive iron uptake by the bone marrow was measured in several patients suspected of having myeloid metaplasia of the spleen.

Liver function studies were made routinely since major hepatic involvement by the underlying disease was considered a contraindication to surgery. The tests included determinations of total serum protein, albumin-globulin ratio, serum bilirubin, alkaline phosphatase, cephalin flocculation, bromsulphalein excretion, and prothrombin time. In some patients, operation was carried out in the face of active liver disease (as shown by needle biopsy) when liver function studies were nearly normal.

More recently, detailed studies of the coagulation system have been carried out in our blood coagulation laboratory. These included determinations which are not performed in the usual workup. While these additional studies were initiated primarily to gain more detailed knowledge of clotting factors in these patients, several important practical benefits accrued. Elevated fibrinolysins were identified in a number of patients and these were successfully neutralized by the use of antiplasmin, a fraction of human plasma or lima bean plasmin inhibitor. Vitamin K_1 oxide was employed to correct prothrombin deficiencies and fresh whole blood for platelet and subfactor deficiencies. This workup proved to be important since the major complications resulted from bleeding tendencies.

The studies listed in the foregoing proved necessary in determining operability and postoperative management. In several instances, serious and irreparable hepatic or bone marrow diseases were defined which contraindicated surgery.

OPERATIVE CONSIDERATIONS

The use of a nasogastric tube prior to and during operation facilitates exposure and decreases the possibility of hemorrhage from the short gastric vessels. Special care in the insertion of the nasogastric tube and endotracheal tube is important since many of these patients exhibit gross bleeding tendencies. Probably the best insurance for a good result is the availability of fresh blood during the procedure and immediately postoperatively. It has been our practice to have available 4 units of fresh blood, drawn within the 12 hours prior to operation, and 2 units of banked blood obtained in the usual manner. The fresh blood is drawn into special plastic bags, designed to preserve platelets.

The left subcostal incision or long left

paramedian incision was employed. For small spleens the former is satisfactory and has the advantage of a lower rate of wound disruption. For large spleens, the left paramedian incision permits better exposure and easier removal of the organ. The thoracoabdominal approach has not been used in this group of patients. The abdomen is explored in the usual fashion, and a careful search for accessory spleens is made at the beginning of the procedure. Curtis and Movitz reported that accessory spleens were found during splenectomy in as many as 31 per cent of cases. In order of frequency, they are found as follows: in the splenocolic ligament, the retroperitoneal space at the under surface of the tail of the pancreas, the gastrocolic ligament, the hilus of the spleen, the splenorenal ligament, the greater omentum, and in tissues overlying the left kidney. If accessory spleens are not removed, hypersplenism may recur. Since the hematologic picture changes rapidly and often soon after ligation of the splenic artery, this is accomplished without delay. This procedure also allows better control of bleeding which may be encountered while dissecting the hilar vessels. A window of adequate size is made in the gastrocolic ligament to accomplish the ligation of the splenic artery coursing along the upper border of the pancreas. Exposure of the pancreas is accomplished by the insertion of retractors; the stomach is retracted upward and the colon downward. The splenic artery is identified by palpation. The artery is usually increased in caliber because of the splenic enlargement and is quite tortuous, particularly in older individuals. The peritoneum at the superior border of the pancreas is incised and a segment of the artery isolated with a blunt right angle clamp. This procedure is carried out as close to the splenic hilum as is conveniently possible. At times the distance from the hilum may be considerable when the patient is obese, when there is marked lymphadenopathy, or when splenomegaly is marked.

The gastrosplenic ligament is divided

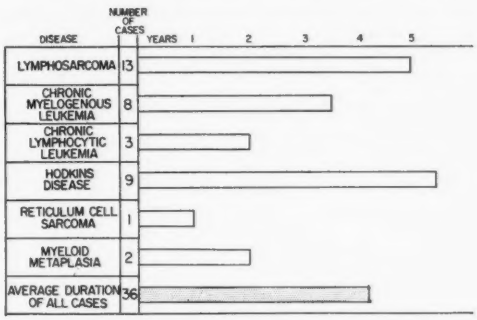

FIG. 1. Average duration of disease prior to splenectomy in 36 patients with lymphoma and leukemia.

after clamping, and the contents of the clamps are carefully ligated. The so-called splenorenal ligament is divided, ordinarily without clamping since this structure is usually avascular. The splenophrenic attachments are divided, careful blunt finger dissection being used. The spleen is carefully rotated toward the midline, and the splenic vessels are individually ligated. The artery is usually ligated before the vein to allow blood sequestrated in the spleen to enter the general circulation. This is aided by gentle massage of the organ. The tail of the pancreas is handled with care to avoid possible injury and subsequent fistula formation. In many of these patients, lymph node involvement in the hilus of the spleen is prominent and thus many of the landmarks are obscured. After the spleen is removed, the operative area is examined carefully for residual bleeding. A warm pack is placed in the splenic bed. Areas of major lymphadenopathy are tagged with silver clips so that future radiation therapy can be administered with greater precision.

The abdomen is thoroughly explored, and biopsies of the liver or of retroperitoneal lymph nodes for diagnostic purposes are often required. The pack in the splenic bed is then removed and the operative area once more examined for bleeding points. A large Penrose drain is placed in the subdiaphragmatic area and brought out through a separate stab wound just beneath the left costal margin. The wound is closed in layers

TABLE II.—HEMATOLOGIC RESPONSE TO SPLENECTOMY

Diagnosis	*No. of cases*	*Preoperative hematologic depression*			*Postoperative hematologic response*			*Operative deaths*
		Severe	*Moderate*	*Slight*	*Good*	*Moderate*	*None*	
Lymphosarcoma	13	8	4	1	10	3	0	
Chronic lymphocytic leukemia	3	2	1	0	1	0	1	1
Chronic myelogenous leukemia	8	3	5	0	1	3	3	1
Hodgkin's disease	9	5	4	0	1	5	2	1
Reticulum cell sarcoma	1	1	0	0	1	0	0	
Myeloid metaplasia	2	1	1	0	1	1	0	
Total	36	20	15	1	15	12	6	3

with running chromic catgut for the peritoneum and interrupted No. 00 silk for the fascia. The skin is approximated with No. 000 interrupted silk.

RESULTS

The immediate postoperative mortality rate was 8 per cent (Table I). Three patients died of massive hemorrhage uncontrolled by re-exploration and vigorous blood replacement. This fact is an expression of the marked disturbances in the coagulation mechanism which these individuals may show. The complication rate was 19 per cent. A patient with myelocytic leukemia was found to have thrombosis of the portal vein at autopsy, 3 months after splenectomy. The platelet level should be observed closely postoperatively. Occasionally, it may rise to a level of 1,000,000 or more. If this occurs, it is wise to initiate the anticoagulant therapy to prevent thrombotic phenomena. Anticoagulants are discontinued when the platelet count declines to near normal levels.

Twenty-two of 36 patients have expired. The average survival time after operation in this group was 8 months (Fig. 2). The longest survivors were patients with lymphosarcoma and myeloid metaplasia, while those with leukemia and Hodgkin's disease had the shortest survival times.

Figure 3 summarizes the survival times of those patients who are living. Since there was only 1 patient in each of the diagnostic categories other than lymphosarcoma, no conclusions can be drawn regarding the relation of postoperative survival to the primary diagnosis.

Table II shows that over 80 per cent of patients had a good or moderate hematologic response to splenectomy. Such a response was defined as (1) significant improvement in one or more of the blood elements showing depression preoperatively, or (2) significant treatability by roentgen-ray irradiation or nitrogen mustard obtained. Six of 33 patients exhibited no response to the operation.

Five patients of the group have shown striking responses to splenectomy. Case summaries of 2 such patients follow.

CASE 1. A 44 year old white male was admitted to the Roswell Park Memorial Institute on 19 July 1956 because of enlarging adenopathy in the neck. In December 1955, generalized lymphadenopathy was found on routine physical examination. In April 1956, an inguinal node biopsy revealed a histologic picture consistent with lymphosarcoma or lymphocytic leukemia. He had received no treatment prior to admission. On admission the patient had generalized lymphadenopathy. The liver and spleen were not palpable. Roentgenogram of the chest showed minimal bilateral hilar adenopathy. A bone marrow aspiration obtained from the sternum was consistent with a diagnosis of lymphosarcoma.

Because of discomfort in the cervical area from lymph node enlargement, he was treated with chlorambucil and steroids. A moderate decrease in adenopathy occurred. In February 1957, because of recurrent enlargement of nodes, roentgen-ray therapy was applied to right cervical region with significant regression of adenopathy. In August 1958, the spleen was palpable for the first time. He received further roentgen-ray therapy to the nasopharyngeal region because of recurrent deafness and dysphagia as the result of lymphoid hyperplasia. In December 1958,

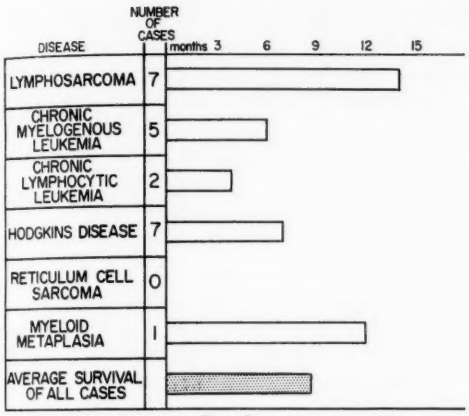

FIG. 2.

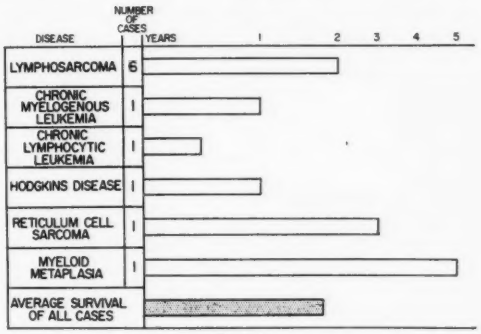

FIG. 3.

Fig. 2. Average survival after splenectomy of 22 patients who are dead.

FIG. 3. Average survival of 11 living patients after splenectomy.

his platelet count dropped to 62,500 per cubic millimeter from a previous normal level. After 2 months of therapy with prednisone there was an elevation of platelets to normal levels. On 25 August, 1959, it was found that the patient's liver and spleen were increasing in size and that he complained of fatigue and sweating. The platelet count at this time was 72,500 per cubic millimeter. On 3 September, he reported a 10 pound weight loss in 7 days and marked increase in symptoms. Generalized petechiae of the skin and mucous membranes were seen. The spleen and liver were moderately enlarged. The hemoglobin was 8.6 grams per cent, the platelet count was 7,500 per cubic millimeter and the white blood cell count was 33,000 per cubic millimeter. His condition appeared to be critical from the standpoint of bleeding, and he was hospitalized.

He had severe epistaxis, gross hematuria, and gastrointestinal bleeding. A sternal bone marrow biopsy on 9 September showed no megakaryocytes, and about 90 per cent of the cells belonged to the lymphoid series. Although bleeding finally subsided, during therapy with ACTH, prednisone, and fresh blood transfusions, the patient's condition was precarious. The platelet count remained at critically low levels and recurrence of hemorrhage seemed imminent. Although the usual diagnostic features of hypersplenism (that is, normal or hypercellular bone marrow) were not present, it was decided to perform a splenectomy in the hope of improving the thrombocytopenia. An uneventful splenectomy was carried out on 23 September 1959. The spleen weighed 1,100 grams. Figure 4 shows the blood picture prior to and after splenectomy. A significant increase in platelets starting on the ninth postoperative day is seen. ACTH and steroids were gradually withdrawn. A bone marrow biopsy on 7 October 1959 showed scattered megakaryocytes. Bleeding did not recur, and the patient was discharged on 9 October. A follow-up bone marrow biopsy was performed on 2 December and showed a moderate number of megakaryocytes with lymphocytic leukemia infiltration. The patient's platelet count was within normal limits in May 1960.

CASE 2. A 54 year old white female was admitted to the Roswell Park Memorial Institute on 15 October 1958 because of weakness, bone pain, and frequent epistaxis. In March 1957, moderate splenomegaly and hepatomegaly were found. A diagnosis of chronic myelogenous leukemia was made on the basis of peripheral blood and bone marrow studies. Prior to admission the patient required 1 unit of blood every 3 to 4 weeks in order to maintain a hemoglobin level of 8.0 grams per cent. She was treated with colcamide in February 1958 and myleran in April 1958. On admission, the patient appeared pale and undernourished. The liver and spleen were moderately enlarged. The results of laboratory work on admission were: hemoglobin 7.5 grams per cent, platelet count 74,000 per cubic millimeter, white blood count, 35,000 per cubic millimeter. The red cell survival with the radiochromium method was 20 days (normal 28 to 40 days). A splenectomy was performed on 29 February 1958. The postoperative course was stormy because of continued hemorrhage. The patient was given 14 units of fresh blood before bleeding was under control. On the seventh postoperative day, the patient became febrile. A mass was palpated in the left flank on 14 November, and a preoperative diagnosis of a left flank abscess was made. An exploratory operation was performed, and hemorrhagic fibrinopurulent peritonitis was found and drained. The culture from the peritoneal cavity was Staphyloccus aureus, coagulase positive. Heavy antibiotic therapy was instituted. The patient showed gradual improvement and was discharged on 25 December 1958. Prior to discharge peripheral blood and bone marrow

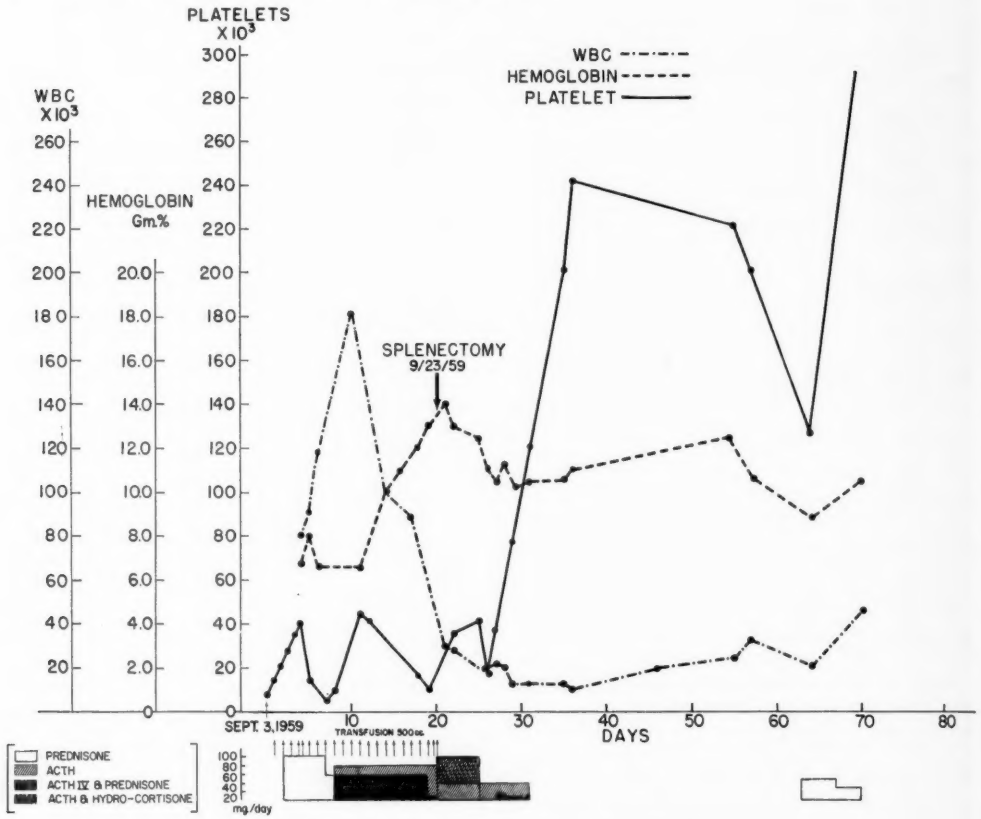

FIG. 4. Blood picture in Case 1 before and after splenectomy.

studies showed that the patient had undergone a complete remission of the leukemia; the hemoglobin was 12 grams, platelet count, 250,000 per cubic millimeter, white blood count, 12,000 per cubic millimeter. This remission persisted until June 1959. At that time she was hospitalized with clinical jaundice. After extensive study, the diagnosis of homologous serum jaundice was made; probably a complication of multiple blood transfusions. The jaundice cleared by July 1959. In September 1959, peripheral blood studies showed evidence of recurring chronic myelogenous leukemia. At 18 months after operation she has not required blood transfusions to maintain a normal hemoglobin level. In May 1960, she was treated with colcamide. She has continued to carry on normal activities.

DISCUSSION

Surgeons have been reluctant to perform splenectomy in patients with lymphomas because of a relatively high operative mortality rate in a procedure which is palliative. While a favorable hematologic response was obtained in 80 per cent of the patients in this series only one-third had significantly long survival times. The basic disease process, rather than the hematologic response per se, appears to govern the outcome. This theory is verified by the fact that the longest survivors were those with lymphosarcoma and myeloid metaplasia, diseases generally considered to have a more favorable prognosis. Patients with Hodgkin's disease and leukemia exhibited not only the shortest survival times but also the highest operative mortality and morbidity. The operation appears to have been of considerable value in one-third of the patients who had un-

expectedly long postoperative survival times. Strikingly favorable responses have been seen after splenectomy.

Case 1 represented secondary hypersplenism which responded specifically to splenectomy. Without operation the patient probably would have died from continued hemorrhage. Case 2 is difficult to evaluate because of the many factors which were involved in the patient's postoperative course. Sporadic reports of remissions in acute myelogenous and lymphocytic leukemia have implicated either a superimposed infection or exchange transfusions. To the best of our knowledge there has been no such remission reported with chronic myelogenous leukemia. Our patient had both an exchange transfusion and a superimposed infection. The secondary hypersplenism in this instance was controlled by splenectomy as evidenced by need for transfusion.

Even those patients whose basic course was not appreciably altered by operation derived benefit in the decreased transfusion requirement, increased roentgen-ray treatability, and removal of painful, often infarcted and markedly enlarged spleens. Twenty per cent of patients showed no hematologic response postoperatively despite laboratory evidence of hypersplenism. This observation may be explained either by failure of a severely infiltrated bone marrow or by the presence of an uncorrected autoimmune hemolytic process. Other, as yet undefined, factors are also doubtlessly involved.

Co-operation between internist and surgeon cannot be overemphasized. Establishing the existence of hypersplenism, the timing of surgery, control of frequently used steroids, and evaluation of coagulation defects are considerations which benefit from such collaboration. The relatively low mortality rate, as compared to other series, may be a product of this close co-operation. The typical patient in this series had far-advanced disease and was refractory to further radiation or drug therapy. Greater benefit from splenectomy might be obtained in patients having earlier disease and showing the first signs of hypersplenism.

SUMMARY AND CONCLUSIONS

1. Thirty-six patients with lymphomas and leukemias who underwent splenectomy for secondary hypersplenism or symptomatic splenic tumor are presented.

2. Eighty per cent showed a favorable postoperative hematologic response.

3. One-third of the group had a relatively long postoperative survival time. Its relation to splenectomy cannot be proved.

4. The mortality rate was 8 per cent and the postoperative complication rate was 19 per cent.

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SURGICAL TREATMENT OF COEXISTING REGIONAL ENTERITIS AND ULCERATIVE COLITIS

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CHRONIC REGIONAL ENTERITIS and diffuse ulcerative colitis are diseases of unknown etiology, and each presents many problems in medical and surgical management. When the two conditions appear in the same individual the treatment becomes even more complicated. That this situation can occur is well known. In a review of 304 patients treated surgically by us at the Lahey Clinic (1) for regional enteritis, 39 (12.8 per cent) also had ulcerative colitis. Twenty-seven of the patients in this group required surgical intervention to control the ulcerative colitis in addition to the operative procedures performed for the treatment of regional enteritis. This experience is reviewed and the results of treatment are summarized.

Both of these diseases occur primarily in the adolescent and young adult with the onset of regional enteritis beginning at a slightly earlier age. The symptoms of regional enteritis began in the second and third decades of life in 28 of the 39 patients. The average age was 27 years. In 26 patients, the symptoms of ulcerative colitis appeared between 20 and 40 years of age with an average age of 32 years.

The sex distribution revealed an incidence of 56.4 per cent (22 patients) in males and 43.6 per cent (17 patients) in females.

In 32 of the 39 patients, the symptoms of ulcerative colitis were not recognized until after the diagnosis of regional enteritis had been established. In 5 patients the onset of symptoms appeared to be simultaneous, and in 2 patients the ulcerative colitis developed first. Of the 27 patients treated surgically for ulcerative colitis, 19 were operated on after surgery had been performed for regional enteritis. Procedures to control both diseases were applied at the same operation in 5 patients, and 3 patients were operated on for ulcerative colitis first.

The average duration of symptoms of regional enteritis prior to surgery was 5.7 years. In contrast, the average duration of symptoms before surgical treatment of ulcerative colitis was 2.9 years. Fifty per cent of the 27 patients treated surgically for ulcerative colitis required operation within 1 year of the onset of symptoms.

The diagnosis of regional enteritis was made on a basis of the history of chronic weight loss, fever, malaise, and cramping abdominal pain. The pain usually followed the ingestion of food and was often associated with frequent, fatty, foul-smelling diarrheal stools. An abdominal mass, fecal fistula, and anorectal disease such as fissure, fistula, or abscess were common findings on physical examination. The diagnosis was confirmed by roentgenograms of the small intestine which revealed increased bowel motility, a narrowed lumen with changes in the mucosal pattern, and, frequently, evidence of an internal fistula.

In the acute phase, the ulcerative colitis began with fever, weakness, dehydration, and abdominal pain. These symptoms were associated with tenesmus and an intractable watery diarrhea containing gross blood and mucus. The disease was characterized by a chronic persistence of symptoms with a tendency toward periodic acute exacerbations. This circumstance eventually led to marked organic changes in the large bowel with

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anemia, malnutrition, and pronounced systemic effects. The proctoscopic examination revealed hyperemia and edema of the mucosa with multiple superficial abscesses which later developed into large coalescing ulcers. Later the mucous membrane acquired the pseudopolypoid appearance typical of chronic ulcerative colitis. On barium enema examination the loss of haustral markings and marked shortening of the colon, due to scarring and thickening of the bowel wall, produced the characteristic "lead-pipe colon."

TABLE I.—INDICATIONS FOR INITIAL OPERATION AT LAHEY CLINIC

Indication	*No. of patients*	*Per cent*
Obstruction	34	87.2
Fistula	11	28.2
Abdominal mass	8	20.5
Perforation (chronic)	4	10.2
Hemorrhage (not associated with ulcerative colitis)	1	2.6
Ulcerative colitis	3	7.7

INDICATIONS FOR SURGERY

Surgical intervention in the management of regional enteritis becomes necessary as the result of the complications of this disease. Partial, intermittent, small bowel obstruction occurred in 34 patients. At the time of admission, 11 patients had fistula formations, 5 of whom had external fistulas, 4 had internal fistulas, and 2 patients were found to have both external and internal fistulas. A palpable abdominal mass was present in 20 per cent of the group (8 patients). Severe, rectal hemorrhage originating from the small bowel occurred only once. Many patients had more than 1 indication for surgical treatment (Table I).

The most frequent indication for surgery in a patient with ulcerative colitis is the failure of medical therapy to control the repeated flare-ups of febrile disease, overwhelming diarrhea, and anal incontinence. This eventually results in marked impairment of nutrition and complete disability. Only 3 patients in the series were operated on for ulcerative colitis prior to surgical treatment of regional enteritis. The incidence of associated rectal problems was 25.9 per cent (10 patients). Five patients had fistula-in-ano, 4 had perirectal abscesses, 2 had anal fissures, and 1 patient had a fistula and an abscess.

PATHOLOGY

Because the etiology of each of these conditions remains obscure, the exact nature of the relationship between regional enteritis and ulcerative colitis is also unknown. A number of investigators have noted striking similarities in the gross visceral changes as well as in the microscopic picture. Other observers believe that these two conditions are entirely separate disease entities. The fact that regional enteritis may involve the colon and ulcerative colitis may extend into the terminal ileum add to the problem.

The differences in the pathologic appearances of these diseases have been emphasized by Warren and Sommers (2-4). In regional enteritis, the entire intestinal wall, its mesentery, and the regional lymph nodes are involved. It appears to start as a granulomatous lymphangitis which causes edema of the intestinal wall and finally cicatrization with fibrosis and muscular hypertrophy. In ulcerative colitis, the early pathologic changes are largely limited to the bowel mucosa and are manifested by shallow, exudative ulcerations which may lead to perforation or, eventually, to pseudopolyp formation and possibly carcinoma. The criteria of Warren and Sommers (2-4) were utilized in verifying the diagnoses in this series of patients. The diagnosis of regional enteritis was substantiated by microscopic examination in 36 of the 39 patients. Including postmortem examination, the presence of ulcerative colitis was demonstrated by pathologic section in 87 per cent of the group.

The terminal ileum was involved by regional enteritis in 35 of 39 patients. Fifty per cent revealed extension of this process to the proximal ileum and distal jejunum.

TABLE II.—SURGICAL TREATMENT OF REGIONAL ENTERITIS (55 OPERATIONS IN 39 PATIENTS)

Type of operation	*Primary operation*	*Second operation*	*Third operation*
Resection of terminal ileum and colon	28	10	3
Resection of small intestine, terminal ileum, and colon	4	1	—
Resection of small intestine	4	2	—
Laparotomy only	2	—	—
Ileocolostomy (bypass without resection)	1	—	—
Total	39	13	3

"Skip areas" were found in 6 patients. In all patients, diffuse involvement of the entire large bowel by ulcerative colitis eventually developed.

SURGICAL TREATMENT

Regional enteritis was treated by radical extirpation of the diseased bowel in 92.3 per cent of the 39 patients. Twenty-eight of these 39 patients had resection of the terminal part of the ileum and right half of the colon, 4 patients had segments of small intestine removed, and, in 4 patients, a combination of the two procedures was performed. In 13 patients one additional resection was required and in 3 patients a third resection was necessary (Table II). In 1 patient with mild regional enteritis, a bypass with an ileocolostomy was performed. Exploratory laparotomy was performed on 2 patients who were found to have too extensive involvement to permit further surgery. A total of 55 operations was performed on the 39 patients with regional enteritis.

Ulcerative colitis was treated by medical management alone in 12 patients. Five of the 12 patients had mild disease and responded satisfactorily to nonsurgical therapy. In the other 7 patients severe symptoms of ulcerative colitis developed in the presence of pre-existing regional enteritis and the patients were too debilitated to withstand a surgical procedure. All of these 7 patients died of their combined diseases (Table III).

Ileostomy without resection of the colon was performed upon 4 patients. Two patients later had a closure of their ileostomy and in 2 a permanent ileostomy was retained without further surgery. Three patients had an ileosigmoidal anastomosis performed after a subtotal colectomy. The most frequently utilized surgical technique of controlling ulcerative colitis was total colectomy with a permanent ileostomy. Twenty patients were treated in this manner. This procedure was staged over 2 or 3 separate hospital admissions. A total of 55 operations was performed on the 27 patients who were treated surgically for ulcerative colitis.

Fifteen postoperative complications were encountered in 110 operations, an incidence of 12.7 per cent. Intra-abdominal abscess and fecal fistula each occurred 5 times. Three of the fecal fistulas were abdominal, 1 was rectovaginal and 1 was enterovesicular. Tetany, resulting from loss of absorptive surface after extensive resection of small bowel, was observed in 2 patients. One wound dehiscence and 1 intestinal obstruction required surgical intervention.

Five deaths occurred following 110 surgical procedures carried out on the entire group. This is an operative mortality rate of 4.6 per cent. Two patients died of peritonitis, and 3 died as the result of progressive inanition, cachexia, and malnutrition. Persistent disease in the intestinal tract was present in all patients who died. The problems presented by the combination of these two serious diseases are well illustrated by the following case history.

ILLUSTRATIVE CASE REPORT

This young man, who later became the coinventor of a well known ileostomy appliance, was 19 years of age when he was first seen in 1944. He had been ill for 18 months with fever, bloody diarrhea, and a weight loss of 60 pounds. A barium enema examination revealed both ulcerative colitis and regional ileitis. In 1945 resection of the terminal portion of the ileum and right half of the colon was carried out because of attacks of small bowel obstruction which were increasing in severity. Improvement was noted, but in 1947 he required an ileostomy and resection of the remainder of the colon and rectum because of uncontrollable rectal bleeding. In 1948 he was again operated on for intestinal obstruction. At that time he was found to have diffuse involvement of the remaining part of the ileum by regional enteritis.

During the next 6 years he was admitted to the hospital many times because of episodes of convulsions and severe prostration due to dehydration, tetany, and electrolyte imbalance. These were brought on by impaired absorption of calcium, potassium, sodium, and chloride as a result of increased activity of his ileitis. On each admission he responded rapidly to intravenous calcium, sodium chloride, and fluid. On 1 occasion he was admitted with jaundice, and a diagnosis of infectious hepatitis was made. Despite large amounts of calcium and salt by mouth, these attacks continued. Because he was well aware of the initial symptoms, he sought relief promptly until his final, fatal episode in 1954 when he died before his tetany, dehydration, and electrolyte imbalance could be corrected.

FOLLOW-UP DATA

In follow-up evaluation these cases have been divided into three groups—good, fair, and poor. Patients classified as having a good result were able to return to a reasonably normal existence. Those falling into the fair result group continued to have either mild persistence of symptoms or infrequent exacerbations. All patients in the third or poor category had a recurrence of severe symptoms, and all eventually died.

Of the 36 patients who required 1 or more bowel resections for regional enteritis, 27 had no evidence of recurrence of this disease during the follow-up period. (Eleven patients had follow-up periods between 1 and 5 years and 16 patients for more than 5 years.) Recurrent disease developed in 9, and the patients died as the direct result of severe enteritis. In 7 of these 9 patients advanced ulcerative colitis was also present. Eight patients died within 6 months of the last surgical procedure.

The patient upon whom a bypass procedure was performed had continuation of mild symptoms of regional enteritis 7 years after operation. Follow-up data on the 2 patients whose surgery was limited to abdominal exploration revealed that one died 9 years postoperatively of combined diseases, while the other had only mild symptoms 5 years after operation.

The results of treatment for ulcerative colitis have been tabulated under the 4 categories by which these patients were managed (Table III). In the group of 12 patients who were managed by medical means alone, 3 were asymptomatic 3, 6, and 8 years respectively after surgical treatment for regional enteritis. Two patients had mild symptoms in 1 to 3 year follow-up periods. The remaining 7 patients died of persistent ulcerative colitis combined with extensive regional enteritis.

TABLE III.—TREATMENT OF ULCERATIVE COLITIS (55 OPERATIONS IN 27 PATIENTS)

Type of management	*No. of patients*	*Results of treatment*		
		Good	*Fair*	*Poor*
No surgery for ulcerative colitis	12	3	2	7
Ileostomy without colectomy	4	1	3	0
Colectomy with permanent ileostomy	20	17	1	2
Partial colectomy with reanastomosis	3	0	2	1
Total	39	21	8	10

TABLE IV.—RESULTS OF COMBINED TREATMENT OF REGIONAL ENTERITIS AND ULCERATIVE COLITIS

Follow-up, years	*No. of patients*	*Results*		
		Good	*Fair*	*Poor*
1– 2	15	3	4	8
3– 4	11	8	2	1
5–10	12	9	2	1
11–20	1	1	0	0
Total No.	39	21	8	10
Per cent		53.9	20.5	25.6

Ileostomy alone gave a fair result in 3 of 4 patients after follow-up periods of 3, 4, and 8 years. Closure of the ileostomy in 2 of these patients was permanent in 1 patient, but the other required a second ileostomy. A good result was obtained in the 1 patient whose temporary ileostomy was closed and in whom symptoms did not recur in a 7 year follow-up period.

Fair results were noted in 2 of the 3 patients who had a subtotal colectomy and ileosigmoidal anastomosis. The follow-up periods were 1 and 7 years. The third patient died within 2 years of persistent disease.

The best results in the management of ulcerative colitis were obtained by total or subtotal colectomy with a permanent ileostomy. Seventeen of the 20 patients treated by this method obtained a good result. All of these 17 patients had follow-up studies for 2 years or more and 9 patients for longer

than 5 years. One patient was classified as a fair result because of mild persistent symptoms on the basis of an enterovesical fistula which was probably due to his regional enteritis.

The combined treatment of regional enteritis and ulcerative colitis produced a good result in 21 patients and a fair result in 8 patients (Table IV). Twenty-two of these 29 patients had follow-up periods for longer than 3 years and 12 patients for more than 5 years.

SUMMARY

A review of 39 patients who were found to have both regional enteritis and ulcerative colitis has been presented. All patients were operated on for regional enteritis, and 27 patients also required surgery for control of ulcerative colitis.

Partial intermittent small bowel obstruction was the primary indication (87.2 per cent) for surgical treatment of regional enteritis. Internal or external fistulas were present in 28.2 per cent and a palpable abdominal mass in 20.5 per cent. The indication for surgical intervention for ulcerative colitis was a failure of medical management to control the disease and to prevent disability or death. Associated perirectal or perianal disease was present in 25.9 per cent.

Regional enteritis was treated by resection of the involved bowel in 92.3 per cent of the patients. A second resection was necessary in 13 patients, and 3 patients required a third resection. After the last resection, 27 of the 36 patients treated by this method had no recurrence of regional enteritis. Sixteen of these patients had follow-up intervals of 5 years or longer without recurrent symptoms.

Twenty of the 27 patients who required operation for control of ulcerative colitis were treated by total colectomy with a permanent ileostomy. A good result was obtained in 17 of the 20 patients and a fair result in 1 patient. All of these patients had follow-up periods of 2 years or more and 10 patients for longer than 5 years.

Fifty-five operations for regional enteritis and 55 operations for ulcerative colitis were performed for a total of 110 operative procedures. The mortality rate was 4.6 per cent (5 operative deaths). Postoperative complications were encountered in 12.7 per cent of the 110 operations. Intra-abdominal abscess and fecal fistula were the most frequent problems.

The results of the combined treatment of coexisting chronic regional enteritis and diffuse ulcerative colitis revealed good results in 21 patients and fair results in 8 patients. A poor result with eventual death occurred in 10 of the 39 patients in this series—a mortality rate of 25.6 per cent. Twenty-two of the 29 patients who obtained a good or fair result had follow-up periods of 3 years or more and 12 patients for longer than 5 years.

CONCLUSIONS

Regional enteritis or ulcerative colitis, occurring alone, presents many problems. The appearance of the two diseases in the same patient greatly increases the difficulties of management. The mortality rate was 25 per cent in this small group of 39 patients.

The indications for surgical intervention are different in the two diseases. Each condition, therefore, must be approached individually as the indications for surgery develop. Resection is considered the surgical treatment of choice for regional enteritis. Surgical management of ulcerative colitis was best accomplished by total colectomy with a permanent ileostomy. The combined application of these two operative approaches was successful in rehabilitating almost 75 per cent of the 39 patients in this series.

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BLEEDING ESOPHAGEAL VARICES IN CHILDREN

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DISSATISFIED with our knowledge of the natural history of bleeding esophageal varices in children and with only 15 cases of our own available for study, we examined the literature for case reports sufficiently detailed to be worthy of analysis. Sixty cases were gathered as a result of this search. The information gained from the study of the total 75 cases is presented in the present article.

In the majority of instances, it is difficult to establish the cause of portal hypertension with bleeding esophageal varices in children. Of the 75 cases, in only 10 was a probable cause noted. Six of the remaining 65 patients were noted to have suffered severe staphylococcal infection such as pneumonia and otitis media during infancy and prior to the development of esophageal varices. Although omphalitis has been incriminated as an etiologic factor in portal hypertension in children, it is obviously difficult to relate positively these two conditions; it is even more difficult to incriminate recurrent bacterial infection or debility. In 1 of our own cases, splenomegaly was noted to follow a difficult exchange transfusion. At 9 months of age, the child had his first bleeding episode (Case 10, Table I).

The site of the obstructive process responsible for the development of portal hypertension and its sequelae was predominantly extrahepatic and in the portal venous system itself. Sixty-eight of 73 cases were examples of extrahepatic portal hypertension (Fig. 1). Of these 68 patients, 2 were noted to have ascites. In only 25 of the 68 cases was the exact nature of the pathologic condition in the portal system identified, either on splenoportogram, at surgery, or on postmortem examination. Twenty-two of these 25 had evidence of disease in the portal vein itself. The remaining 43 cases were classified as examples of extrahepatic portal hypertension on the basis of normal liver function studies or normal liver biopsies. This high incidence of extrahepatic obstruction, with involvement of the portal vein itself, makes it frequently impossible to perform direct portacaval anastomosis in the treatment of these children.

Factors of importance to the surgeon in establishing a program of management for these patients are the age at the time of first bleeding, the mortality during the first bleeding episode, and the over-all mortality in those children followed up without surgery.

The first bleeding episode occurred before 7 years of age in more than 70 per cent of the children in this series (Fig. 2). This is a factor of considerable importance in the surgical management of this disease when it is realized that splenorenal shunt is rarely successful in children under 60 to 70 pounds in weight, about 10 years of age, because of the small size of the shunt and therefore the high incidence of thrombosis.

In 26 patients the interval between first and second bleeding episodes was known. Eighty-eight per cent of these bled massively within 2 years of the first bleeding episode. No patient died during the first bleeding episode. Of 42 patients followed up to a second bleeding episode without surgery, only 1 died of the second hemorrhage, and that 6 years after the first hemorrhage. This low mortality during the first and second bleeding episodes makes it possible to delay operation, at least until after the second episode, thus allowing the patient to approach that size at which splenorenal shunt

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TABLE I.— SUMMARY OF 6 CASES OF ESOPHAGOGASTRECTOMY WITH COLON INTERPOSITION, CHILDREN'S HOSPITAL, LOUISVILLE

Case No.	*Intra-hepatic disease*	*Extra-hepatic disease*	*Age at first bleeding*	*No. of bleeding epis. before first op.*	*Age at first op.*	*First operation*	*Multiple procedures*	*Age at colon inter-position*	*Final status and comment*
1		X	3 yrs.	None	1 yr.	Splenectomy	Colon inter-position	10 yrs.	Splenectomy for Banti's anemia. Last hemorrhage, 6 mos. preop., required 3,000 c.c. blood transfusion. Doing well 9 months postop.
3	X		2 yrs.	2	2½ yrs.	Splenectomy and colon inter-position		2½ yrs.	Major disease was obstructive biliary cirrhosis. Poor surgical candidate. Died 3 mos. postop. of leak at esoph.-colon anastomosis.
6		X	7 yrs.	2	7 yrs.	Splenectomy elsewhere	(2) Transection of stomach (3) colon interposition	13 yrs.	Bled every 3-4 mos. before colon interposition. At 36 mos. postop. doing well, no bleeding.
8	X		2 yrs.	3	2½ yrs.	Colon interposition		2½ yrs.	Did well for first 3 mos. postop. Died suddenly 3 mos. postop. at home, cause unknown. No bleeding.
10		X	9 mos.	3	10 mos.	Colon inter-position		10 mos.	At 2 mos. postop. adhesive obstruction, adhesions to spleen. Splenectomy, 8 mos. postop. marked abdominal distention, nutrition problem.
11		X	7 yrs.	2	8½ yrs.	Splenectomy elsewhere	(2) Explor. and removal portal lymph node (3) colon interposition	15 yrs.	Bled 3 to 4 times a year prior to operation. At 12 months postop. doing well.

can be expected to provide good results. Despite this low initial death rate, there was a 21 per cent mortality among 28 patients followed up for 3 years without surgery; although this mortality may have diminished with our better understanding of the benefits of transfusion, surgery would appear to be indicated shortly after the second major bleeding episode.

Although primarily interested in the natural history of the disease process, we were able to confirm the opinions of others relative to the value of various surgical procedures utilized in the treatment of bleeding esophageal varices in children. These patients had a total of 89 operations; over half had splenectomy as their first operative procedure.

Splenectomy proved to be of little value. Splenorenal shunt under correct circumstances proved to be of most value. Various other procedures have been developed in an attempt to treat the patient who is either too small for the performance of splenorenal shunt, who has had prior operations making splenorenal shunt impossible, or in whom splenorenal shunt has failed.

Insufficient information is available to define satisfactorily the place of anastomosis of inferior vena cava to superior mesenteric vein in the treatment of bleeding esophageal varices in children. Transthoracic ligation of the esophageal varices is at best a temporary method of handling the problem and, in our hands at least, an unsatisfactory technical maneuver in small children. Esophagogastrectomy and primary esophagogastrostomy we object to because of the well known susceptibility of the esophagus to the gastric juices with resultant esophagitis. We are interested in esophagogastrectomy with interposition of isolated transverse colon between

esophagus and stomach in the treatment of this group of children unsuited for splenorenal shunt and have performed this procedure 6 times in the past 3 years with 1 operative death (Table I). With this procedure we know that the site from which bleeding is taking place has been removed. Of course, in the interposed colon having the same venous drainage as the esophagogastric junction, further varices may well develop as time goes by. Whether or not acid peptic digestion will result in the erosion of these varices is a matter that will have to await further evaluation. It is possible, but by no means certain, that bleeding may be delayed long enough for the development of sufficient general collateral circulation to result in a drop of the intraportal pressure. In view of the short follow-up periods available for our study in this group of patients, we make no recommendations favoring this surgical procedure which is utilized in treating what is at best a desperate situation. In evaluating the benefits of surgery, it is worth noting that recurrent postoperative bleeding took place within 3 years in over 90 per cent of patients available for such a study.

Twenty-five of these 75 patients died, 23 as a result of their disease and 2 of unrelated diseases. Sixty per cent of the mortality was related directly to hemorrhage and 32 per cent were operative deaths. The mortality rate from hemorrhage has dropped from a level of 30 per cent before 1940 to a level of 10 per cent since 1940. Danger of death from bleeding obviously still exists, although this hazard has been considerably reduced as a result of our increased knowledge of the benefits of blood transfusions and possibly by the introduction of esophageal tamponade.

Of 8 operative deaths, 2 were in patients with intrahepatic disease and 3 in patients subjected to extensive emergency surgery for the treatment of their bleeding. Of the 75 cases under consideration, only 4 patients underwent extensive emergency operations for the treatment of their disease and 3 of the patients died as a result of their operations.

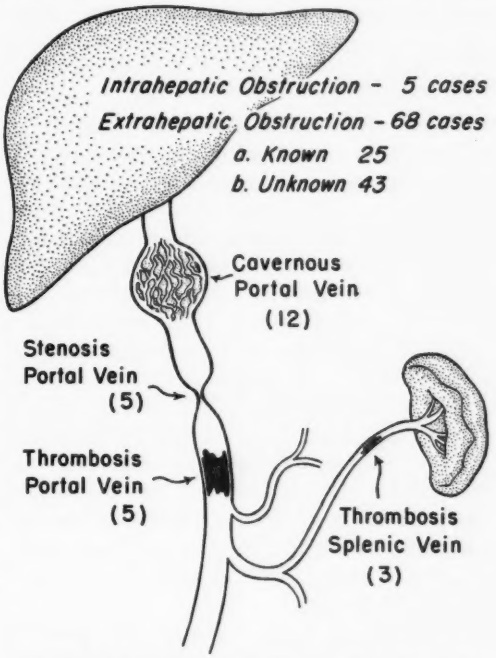
Intrahepatic Obstruction - 5 cases
Extrahepatic Obstruction - 68 cases
a. Known 25
b. Unknown 43
Cavernous Portal Vein (12)
Stenosis Portal Vein (5)
Thrombosis Portal Vein (5)
Thrombosis Splenic Vein (3)

FIG. 1. Nature of disease in 73 cases. Note that ascites was observed in only 2 cases of extrahepatic obstruction.

With the knowledge thus gained concerning the natural history of the disease process, we have formed for ourselves a flexible program which we hope may prove of benefit in the handling of this problem.

The majority of these patients will have stopped bleeding on admission to the hospital or shortly thereafter and require only blood replacement before a definite therapeutic program is decided upon. Only a

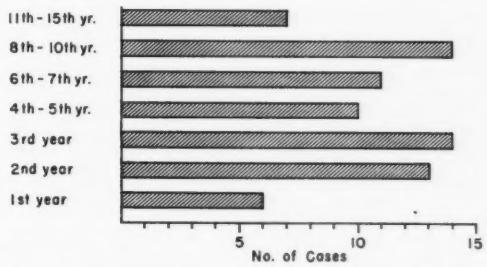

FIG. 2. Age at first bleeding episode in 75 cases. Note that 72 per cent of patients were less than 7 years old at first bleeding.

few children will require esophageal tamponade. There is in our opinion no place for emergency surgery in the treatment of these children.

Most of the patients in this group have extrahepatic obstruction, the liver is not diseased, and the problems attendant on a diseased liver are rarely present. The diagnosis of portal hypertension with bleeding esophageal varices due to extrahepatic disease is verified by normal serum proteins, bromsulphalein, and prothrombin activity, together with roentgenographic evidence of the presence of esophageal varices both by esophagram and splenoportogram. In the light of the low mortality attendant on the first and second major hemorrhages in this group we allow the patient to carry on until after the second bleeding episode, and then consider operating upon the child 1 month after the cessation of bleeding.

At this point in management, the question of definitive surgical therapy arises. In general, it is agreed that portal systemic decompression is the treatment of choice in all types of portal hypertension with bleeding esophageal varices and that, of the various maneuvers available, portacaval shunt appears to be most effective. Unfortunately, because of the high incidence of involvement of the portal vein itself in this malady in children, portacaval shunt is not often a feasible procedure. Splenorenal shunt therefore appears to be the most satisfactory method of achieving portal systemic decompression in children, but not until about their tenth year of age.

The patient 6 years of age or less at the time of the first bleeding presents the most difficult problem. The patient is most likely to bleed again within 2 years and subsequently to bleed frequently, perhaps every 6 months. Splenorenal shunt at this age is not worthwhile. The difficulties inherent in maintaining such a patient without operation until the age of 10 are obvious, necessitating repeated hospital admissions and multiple blood transfusions; therefore some other form of surgical therapy is indicated. Probably the two procedures to be considered are ligation of esophageal varices, or esophagogastrectomy with colon interposition. For reasons already indicated we elect to utilize esophagogastrectomy with colonic interposition in the treatment of this group of patients.

A child more than 7 years of age at first bleeding is near enough to the age, 10 years, or weight, 60 to 70 pounds, at which splenorenal shunt is possible that it would seem worthwhile continuing conservative measures until he is ready for surgery. However, should splenorenal shunt fail, esophagogastrectomy with interposition may be attempted.

SUMMARY AND CONCLUSIONS

As a result of an analysis of 75 cases of portal hypertension with bleeding esophageal varices in children, 15 cases from the Children's Hospital, Louisville, and 60 drawn from the literature, we have obtained the following information:

1. The majority of these patients, 88 per cent, had extrahepatic disease. Of 25 patients with extrahepatic disease in whom the exact pathologic cause was identified, 22 had disease involving the portal vein itself, making portacaval anastomosis almost an impossible therapeutic maneuver.

2. Over 70 per cent of these patients bled the first time before they were 7 years of age. There were no deaths during the first bleeding episode.

3. The natural history of the disease is that of repeated hemorrhages after the first bleeding episode. Of the 42 patients allowed to bleed on 2 occasions before surgery only 1 patient died as the result of hemorrhage.

4. In this group of patients, the mortality from hemorrhage in 28 patients followed up for 3 years after their first bleeding episode without surgical intervention was 21 per cent, 6 patients. This mortality from hemorrhage, however, has been much lowered since 1940.

5. Operative treatment appears to be an essential part of the successful management of portal hypertension with recurrent bleeding from esophageal varices. Emergency operation appears to be unnecessary and unwise in this condition.

6. Splenectomy is not an effective method of handling bleeding esophageal varices with portal hypertension.

7. The most satisfactory method of achieving portal systemic decompression is splenorenal shunt. This operation would appear to be of no value before the age of 10 years or in children under 60 to 70 pounds of weight.

8. Esophagogastrectomy with interposition of colon may prove to be a satisfactory and definitive method of handling those children too small for a successful splenorenal shunt or those children whose prior operation makes splenorenal shunt impossible.

ACID-BASE BALANCE IN SURGICAL PATIENTS

II. The Dynamic State of the Equilibrium

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THE PURPOSE in this paper is to point out the dynamic state of acid-base balance that may exist in some surgical patients. In a survey of acid-base disturbances in 62 selected surgical patients reported previously (3), each case was represented by a single set of observations selected for presentation according to the degree of abnormality of the *p*H value. Such a method of presentation depicts a static state and creates an impression that may be erroneous, for, although the *p*H of the extracellular fluid is found to be relatively stable in health, it is exposed during anesthesia, operation, and convalescence to many deranging influences and may hold steady or yield. Changing conditions are illustrated, discussed, and to some extent explained.

To illustrate the dynamic state of acid-base balance that may be associated with major operations or trauma and the interplay of factors controlling this equilibrium, observations obtained seriatim on 2 patients are presented. The parameters are the *p*H, the whole blood buffer base, the partial pressure of carbon dioxide, and the oxygen saturation of the arterial blood. Each sample satisfactorily obtained and analyzed for these components is referred to as an "observation." Data are presented in a graphic form utilizing buffer diagrams previously described and explained (11). The variations in buffer patterns are the result of physiologic and physicochemical factors. Among the former are the numerous physiologic mechanisms concerned with compensations; among the latter are the modifications of the anion equivalency of the blood proteins with *p*H changes. Included also for comparison are some correlated data concerning the serum electrolytes, arranged in ionic patterns according to the method of Gamble.

The whole blood buffer base $(B_B^+)_b$, expressed in milliequivalents per liter, represents the metabolic component. This is the numerical expression of the "buffer ions," anions capable of accepting H^+ ions within physiologic range. Included are bicarbonate, hemoglobin, serum protein, and inorganic phosphate. The anion equivalency of hemoglobin (H_b^-) is proportional to (a) the hemoglobin concentration, (b) hemoglobin oxygenation, and (c) the *p*H of the blood, increasing with alkalinity.

The $(P^-)_b$ is the anion equivalency of the serum protein and serum inorganic phosphate; its value depends upon (a) the concentration of albumin and globulin, (b) the *p*H of the extracellular fluid, and to a minor extent (c) the amount of phosphate ion. In the presence of a low hematocrit this value is relatively increased; with a high hematocrit it is relatively diminished.

The bicarbonate $(HCO_3^-)_b$ value is of great importance because it is a form of carbon dioxide, a substance which is abundant, widely distributed, part of an efficient "buffer system," and subject to delicate control by respiratory and renal excretory mechanisms. Endogenous carbon dioxide is of metabolic origin; 400 to 600 liters are produced daily; 17 liters are stored in soft

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tissue and 100 liters in bone. It combines reversibly with water to form carbonic acid, a weakly dissociated acid, part of the bicarbonate-carbonic acid buffer system which is described by the classical Henderson-Hasselbalch equation. Within the body are numerous buffer systems which must remain in mutual equilibrium though each has its individual characteristics. Therefore, knowledge of the bicarbonate-carbonic acid system, the easiest to measure, provides information concerning all of the buffer systems.

Renal mechanisms provide the fundamental control of the concentration of bicarbonate ion in the extracellular fluid. In addition, the properties of carbon dioxide which enable it to be promptly transported to the lungs and quickly released into the alveoli endow the bicarbonate-carbonic acid system with unique flexibility and great responsiveness to metabolic changes. Carbon dioxide moves readily across the cell membrane resulting in shifts of other ions, most notably the chloride shift. Frank loss of cation, usually Na^+, or increase in anion, usually Cl^-, produces a fall in bicarbonate; loss of Cl^- or gain in total cation has an opposite effect.

The most important factors recognized as modifying the level of the bicarbonate ion (HCO_3^-) in the extracellular fluid may therefore be listed in the following categories: (a) renal regulation; (b) respiratory output of CO_2; (c) buffer mechanisms; (d) linked ionic transfers (H^+, Na^+, Cl^-, HCO_3^-); (e) acquisition of exogenous CO_2 or precursor substances; (f) cation-anion gains or losses; and (g) rate of production of endogenous CO_2.

The respiratory component of acid-base balance is related to the concentration of carbonic acid which varies directly with the partial pressure of carbon dioxide (P_{CO_2}). Ventilatory and respiratory functions control the carbon dioxide tension of the arterial blood (Pa_{CO_2}) which is in appropriate equilibrium with the alveolar carbon dioxide tension. The Pa_{CO_2} value is subject to rapid or subtle change and can be affected by the following: (a) primary pulmonary function; (b) thoracic cage function and action; (c) airway patency; (d) value of $(HCO_3^-)_a$; and (e) chemoreflex control of ventilation.

The latter is emerging as of hitherto unsuspected importance to the clinician because the basic regulatory mechanisms, largely dependent upon arterial *p*H, Pa_{CO_2}, and Pa_{O_2}, may be significantly modified by endogenous products of metabolism, hormones, drugs, disease, pain, unusual losses or gains, and many other factors influential during anesthesia, operation, and convalescence.

Thus, arterial *p*H is the vector sum of these many factors. Variations in respiration can produce rapid alterations of the respiratory component and, thereby, of arterial *p*H. Relatively, the constituents of the metabolic component move more slowly. Optimal management is dependent upon the recognition, quantitation, and evaluation of the nature of an imbalance. The accuracy and precision with which this can be accomplished indicates the particular value of the method.

METHODS

Arterial blood was used for the determination of *p*H, hematocrit, and gases. Heparin solution was used to fill the dead spaces of the syringes which were sealed with mercury-filled caps. The syringe used for the *p*H determination was prewarmed and reimmersed immediately in a thermos bottle containing water at 38 degrees C.; determination was made within 3 minutes of collection. The *p*H was determined with either a Beckman *p*H meter and glass electrode vessel with suitable temperature controls or the Cambridge research model *p*H meter with a water-jacketed electrode assembly maintained at 38 degrees C. By these means glycolysis was avoided, anaerobic conditions were maintained, and temperature was controlled. The carbon dioxide content, oxygen content, and oxygen

capacity of blood were determined by the method of Van Slyke and Neill except in instances when ether anesthesia required the method of Goldstein and associates. The methods for the determination of hematocrit and serum constituents have been described (3, 10). The bicarbonate concentration of arterial serum was obtained from the nomogram of Singer and Hastings (9). In some instances, as dictated by expediency, venous blood was used for the determination of serum electrolytes, and the carbon dioxide combining power was used as a measure of its bicarbonate concentration. The whole blood buffer base and partial pressure of carbon dioxide of the arterial blood were obtained from the nomogram of Singer and Hastings. The whole blood bicarbonate $(HCO_3^-)_b$ was calculated by means of the following equation:

$$(HCO_3^-)_b = (CO_2)_b - \left[(H_2CO_3)_s\,(1-Vc) + (H_2CO_3)_c\,(Vc)\right]$$

where $(CO_2)_b$ is the whole blood carbon dioxide in millimols per liter, $(H_2CO_3)_s$ is the carbonic acid concentration of the serum which is obtained from the nomogram, Vc the hematocrit expressed as a decimal, and $(H_2CO_3)_c$ the carbonic acid concentration of the red blood cells. The latter was calculated by the equation of Dill and associates, $(H_2CO_3)_c = 0.0362\ (Pa_{CO_2})\ (.72)$ where Pa_{CO_2} is the partial pressure of carbon dioxide. The anion equivalency of $(Hb^-)_b$ was calculated as the sum of that contributed by the oxygenated and reduced forms at the observed *p*H from the data in Table IV of Singer and Hastings (9). The anion equivalency of the serum protein and serum inorganic phosphate per liter of whole blood $(P^-)_b$ was calculated by the equation:

$$(P^-)_b = (B_B^+)_b - \left[(HCO_3^-)_b + (Hb^-)_b\right]$$

where $(B_B^+)_b$ is the whole blood buffer base and the other notations are as previously given. The diagrammatic representation of these parameters was that previously reported from this laboratory (11); in the ionograms of the serum constituents, rectangles without specific values denote undetermined constituents and normal values were assumed in their construction.

Normal values are given in the diagrams at the left of each figure. Normal range for arterial blood *p*H is considered to be between 7.36 and 7.46.

CASE REPORTS

Case 1. (Fig. 1). A 60 year old man had been treated for 12 years because of intermittent stricture of the posterior urethra. In the past 2 months bladder capacity and force of stream had been steadily diminishing. Cystoscopy disclosed an extensive bladder tumor.

On 4 November total cystectomy with bilateral ureterosigmoidostomy was performed. Wound dehiscence occurred on the third postoperative day, and closure was accomplished with wire sutures. After this procedure the patient became nauseated with vomiting and hiccoughs. Two days after the secondary wound closure a gastric tube was inserted and suction was applied. Decreased breath sounds were noted over the right side of the chest, and a film disclosed linear atelectasis in both lung fields. There was a large amount of gastric drainage for 3 days; then the tube was removed and oral fluids were instituted. During the first 6 days after the initial operation, intravenous intake consisted of 12.5 liters of glucose in water and 1.5 liters of normal saline. During the subsequent 3 days 2,000 to 3,000 milliliters of normal saline were given daily.

On 13 November he was markedly dehydrated and lethargic with gasping respirations, a pulse rate of 140, and blood pressure of 65/40 millimeters of mercury. Films of the abdomen were consistent with small bowel obstruction. Samples of arterial blood were drawn. A plastic catheter was inserted into an arm vein, through which the patient received 4,000 milliliters of glucose in water, 160 milliequivalents of potassium and two blood transfusions. Oxygen administration was begun, and a long intestinal tube was placed in the upper small bowel.

The clinical response to treatment was favorable. Parenteral alimentation during the next 3 days included protein hydrolysate, alcohol, 10 per cent glucose, serum albumin, blood, and 750 milliliters of 1/6 molar sodium lactate.

After intestinal drainage of 2,000 milliliters in the next 24 hours, the abdomen became soft, the tube was clamped, and oral fluids were accepted. Oxygen was discontinued.

The patient's general condition on 16 November was much improved and oral intake was increasing.

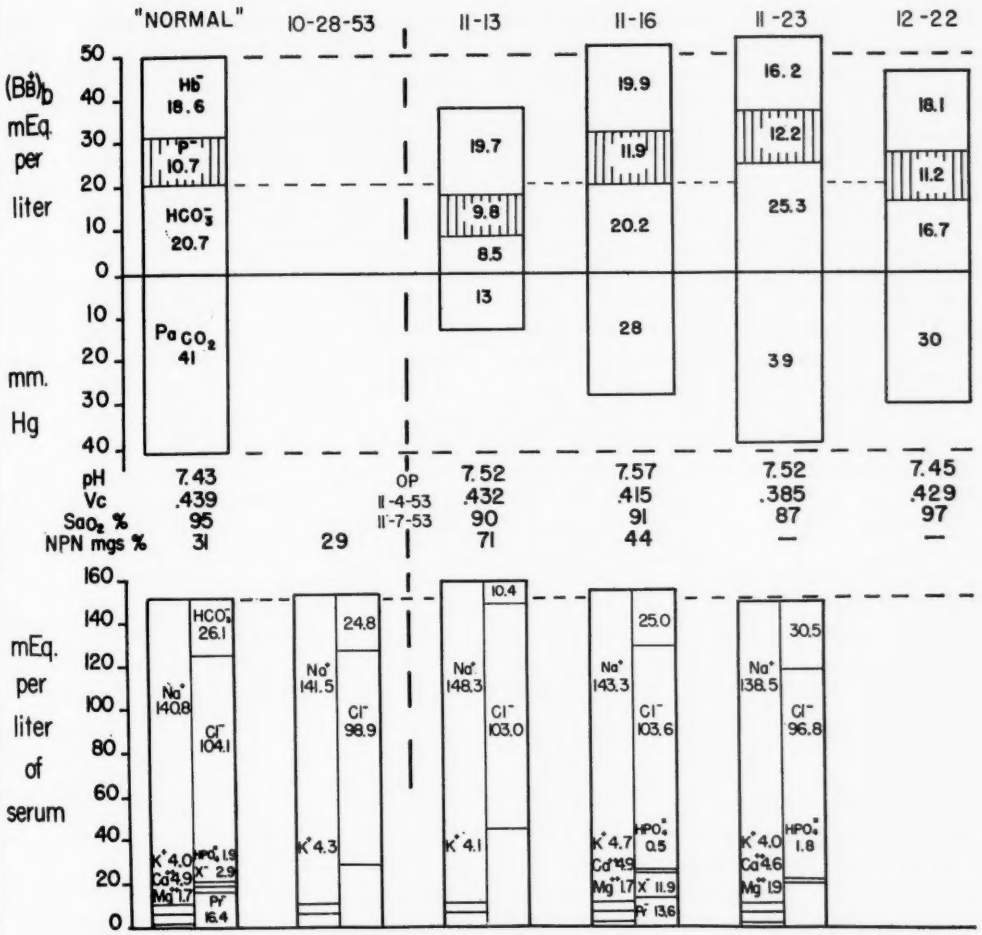

FIG. 1. Case 1. Arterial blood acid-base balance and serum electrolyte patterns of a 60 year old man with total cystectomy, implantation of the ureters into the sigmoid, wound dehiscence, and intestinal obstruction. The vertical interrupted line labelled *OP* denotes day of operation. $(B_B^+)_b$ is the whole blood buffer base, Pa_{CO_2} the partial pressure of carbon dioxide, Vc the hematocrit, and Sa_{O_2} the oxygen saturation. Hb^- is the anion equivalency of hemoglobin, P^- that of the serum proteins and inorganic phosphate, and HCO_3^- that of the blood bicarbonate. All are expressed as milliequivalents per liter of whole blood.

Two days later a vigorous attempt was begun to maintain the increased bicarbonate content of the serum. Sodium bicarbonate, 18 grams, was given daily for 5 days and, in addition, a liter of 1/6 molar sodium lactate daily for 3 days.

The patient was taking fluids and light diet by mouth on 23 November. He was up and about the ward and doing relatively well except for some wound sepsis. Sodium bicarbonate was discontinued after studies revealed high bicarbonate value.

By 22 December, convalescence had continued irregularly. There were wound difficulties attributable to persistent infection in poorly drained pockets. In addition, periods of abdominal cramps, distention, hiccoughs, nausea, and vomiting occurred requiring intravenous alimentation, occasional gastric intubation, and other therapeutic measures of great variety. Such an episode began 19 December and lasted several days; administration of oxygen was begun on 20 December and continued through the twenty-second at which time the arterial blood sample was drawn.

On 13 November, the day the first arterial acid-base observation was made, one might justifiably have expected acidosis in this patient with cystectomy and both ureters transplanted to the colon 9 days before. The postoperative course had been stormy, with inadequate intake and some gastrointestinal losses. He appeared terminal with deep gasping respirations, a hypotension of 65/40, and tachycardia, with a pulse rate of 140. The whole blood and serum bicarbonate values were low, and the nonprotein nitrogen was elevated, laboratory findings usually associated with acidosis. When actually measured, however, the *p*H was distinctly alkaline, 7.52, the product of a disproportionately low Pa_{CO_2} from hyperventilation.

Three days later, with marked clinical improvement and normal values for blood and serum bicarbonate, the extent of the alkalosis was increased to *p*H 7.57. On this occasion the alkalosis appeared to be mainly, but not entirely, a result of hyperventilation, even though the Pa_{CO_2} had risen from 13 to 28 millimeters of mercury. Large amounts of biologically alkalinizing substances by mouth and vein further increased the blood bicarbonate, the *p*H on 23 November moved toward normal because hyperventilation decreased, and the buffer pattern of metabolic alkalosis was produced. After a month of "doing poorly," until 22 December, during which time parenteral alimentation was frequently necessary, and with little additional sodium bicarbonate, the patient had a normal arterial *p*H, but an abnormal blood buffer pattern continued.

The marked variability of ventilation is puzzling but is probably related to factors influencing the chemoreflex control. A low arterial oxygen tension presumably was important but not dominant, for, though it is calculated[1] to be consistently low at the first three observations, 54, 54, and 47 millimeters of mercury, the Pa_{CO_2} ranged widely from 13 to 39 millimeters of mercury.

[1]Calculated from arterial oxygen saturation utilizing oxygen dissociation curve for human blood based on data of D. B. Dill.

Comparison of the blood buffer pattern in this man with the normal reveals both a decrease and an increase, 38 to 54 milliequivalents per liter, in the total value. The changes are mainly, but not solely, in the bicarbonate compartment. $(Hb^-)_b$ drops from 19.9 to 16.2 milliequivalents per liter between 16 and 23 November owing to (1) lower hematocrit, (2) a fall in the *p*H, and (3) decreased oxygen saturation. $(P^-)_b$ ranges from 9.8 to 12.2 milliequivalents per liter. Its value varies inversely with the hematocrit, modified somewhat by the *p*H and the value of the phosphate ion, which when measured on 16 November was at an extremely low level of 0.5 milliequivalent per liter compared with the normal of 1.9.

The buffer diagram indicates the acid-base disturbance to be largely confined to the bicarbonate-carbonic acid system, for both components are quantitatively markedly reduced, but the ratio is also abnormal with a disproportionately low Pa_{CO_2} from hyperventilation. A full explanation is conjectural, but one must consider the influence of starvation, renal dysfunction, gastrointestinal losses, hyperventilation, fluid administration, and reabsorption by the colon of substances excreted in the urine. The role of the bicarbonate buffer system under a great range of circumstances is hereby illustrated; the equilibrium is clearly defined by the familiar Henderson-Hasselbalch equation:

$$pH = 6.10 + \log \frac{[BHCO_3]}{[0.301 \times P_{CO_2}]}$$

CASE 2. (Fig. 2). A 61 year old man entered the hospital with a history of bloody stools for 3 months and a rectal mass discovered by his physician a few days before. Throughout both lung fields were inspiratory and expiratory wheezes and rhonchi which changed little with coughing. A clinical diagnosis of chronic bronchitis and emphysema was recorded. A routine roentgenogram of the chest was reported as negative, and no pulmonary function studies were requested.

On 12 June abdominoperineal resection was performed under pentothal, nitrous oxide, and ether anesthesia.

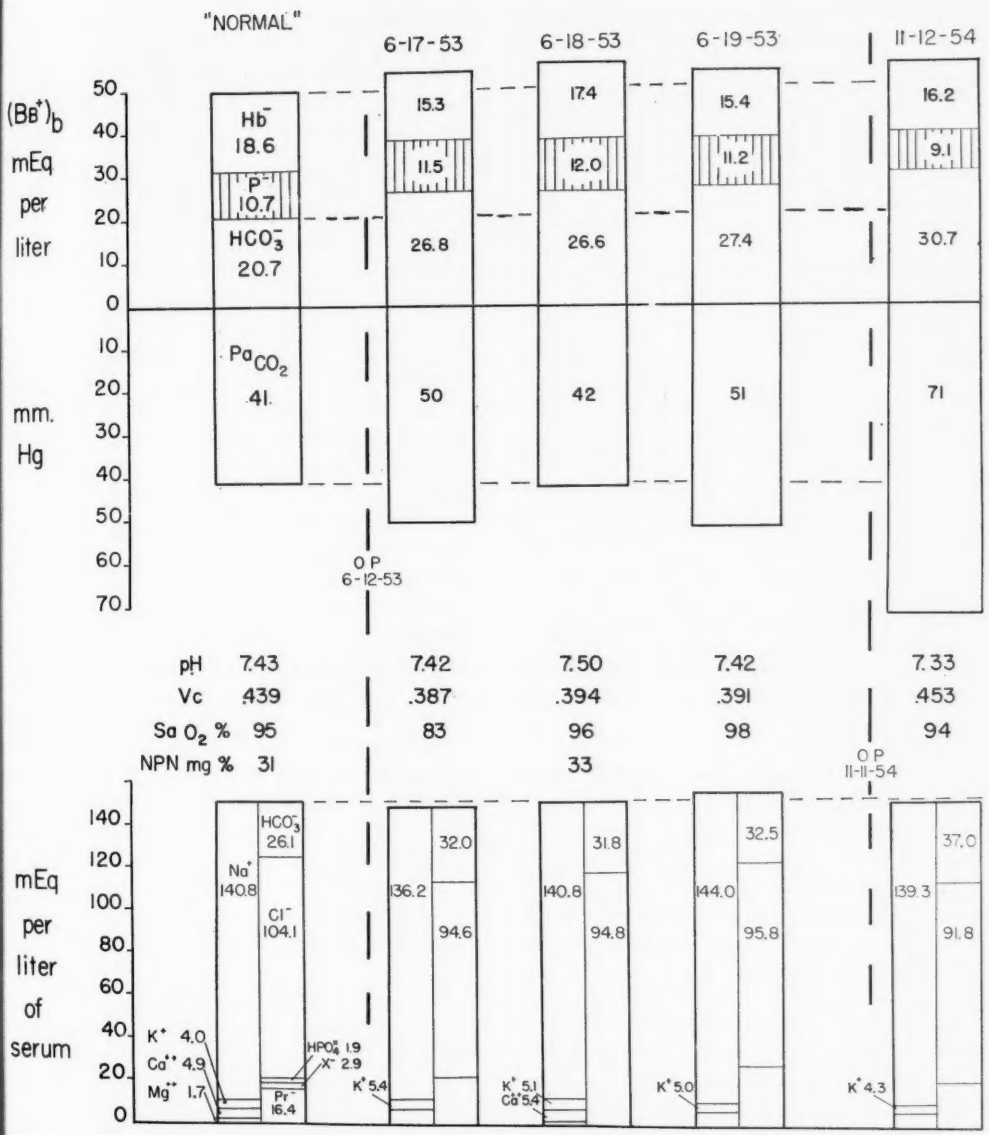

FIG. 2. Case 2. Arterial blood acid-base balance and serum electrolyte patterns of a 61 year old man with carcinoma of the rectum who was studied on two occasions: the first after his abdominoperineal resection when he had marked ileus; the second, 1½ years later as he underventilated while recovering from anesthesia and shock subsequent to resection of gangrenous small bowel. For explanation of the symbols see Figure 1.

The postoperative course for 5 days was marked by ileus and some pneumonostasis of both lungs, with recent development of mental confusion. Included in the intravenous alimentation on 14, 15, and 16 June were 1,000 cubic centimeters of an electrolyte solution containing 70 milliequivalents per liter of ammonium ion.

On 18 June he was receiving oxygen and had been for the previous 24 hours. The abdomen was softer and less distended, but there was an increase in the

mental confusion and the onset of auditory and visual hallucinations. The nursing notes of the early morning hours observe that he was "forcibly hyperventilating." Blood ammonia was 66 micrograms per cent of ammonia nitrogen, 3 minutes after shedding, compared with a normal of 36 micrograms per cent. The long intestinal tube had passed into the jejunum.

On 19 June, mental confusion persisted with hallucinations and restlessness. Oxygen administration was continued. The long intestinal tube was midway down the small bowel, draining well.

He gradually improved, and further convalescence was unremarkable until 2 months after operation when homologous serum jaundice developed for which he was hospitalized for 2 months with satisfactory recovery. He returned to farming and was well until 1½ years after operation when he suffered severe, crampy, periumbilical pain that persisted, and he entered the hospital 24 hours later.

On 11 November under pentothal, anectine, nitrous oxide, and ether anesthesia exploratory laparotomy revealed a long segment of strangulated jejunum from a volvulus around adhesive bands, and 100 centimeters of bowel were resected. During the immediate postoperative period his blood pressure was unstable in spite of transfusion of 2,000 cubic centimeters of blood. In the recovery room the foot of the bed was elevated approximately 23 centimeters, and oxygen was administered at the rate of 5 liters per minute. Arterial puncture was performed after 8 hours in this position.

The first observation was made on the fifth postoperative day because the patient was clinically sick and aid was needed for management. There was oxygen unsaturation, carbon dioxide accumulation, and bicarbonate elevation, a pattern typical of the chronic respiratory cripple with pulmonary fibrosis and emphysema who is able to compensate for carbon dioxide retention by renal mechanisms and maintain a normal *p*H.

On 18 June it was found that, in spite of oxygen administration, with consequent normal oxygen saturation, Pa_{CO_2} had fallen significantly, creating a distinct alkalosis in the presence of a stable whole blood bicarbonate. With reason, one would expect a rise in Pa_{CO_2} with suppression of the hypoxic drive after correction of a low oxygen tension. One might even have been tempted to cover this anticipated rise by sodium bicarbonate administration, which would have increased still further the degree of alkalosis. The cause for the increased ventilation is, as is usually the case, speculative, but may be attributed to the increased psychomotor activity or elevated blood ammonium.

On the following day the oxygen saturation was found to be maintained by continued supplementation; the Pa_{CO_2} had returned to an abnormally high level, but a normal *p*H had been achieved in the presence of a continued elevated blood bicarbonate from renal reabsorption of $NaHCO_3$. Serum potassium levels were never found depressed, so that primary metabolic alkalosis was not considered therefore to be the basic cause of these buffer patterns.

At the fourth observation, nearly 1½ years later, oxygen saturation had been maintained by supplementation, there was acidosis, and the pattern was again that of respiratory insufficiency, somewhat more severe and without adequate buffering.

A logical explanation for the excessive carbon dioxide accumulation is proposed:

Although baseline studies were not obtained, it is likely that this man had a pulmonary functional reserve that was marginal. Ventilation was compromised by the head-down position; neuromotor activity was suppressed by drugs; the chemoreflex drive of low arterial oxygen tension, often important in such circumstances, was not operative.

It is interesting to note again the unreliability of the bicarbonate levels in assessing blood *p*H, this time in reverse, for acidosis exists in the presence of a high level.

DISCUSSION

The changes in the blood and serum, here reported, are considered to be the result of many factors. There is a background against which they should be evaluated, the metabolic response to trauma and operation. Superimposed upon these changes of a generalized nature, which vary considerably from one person to the next, are the effects

of particular diseases, complications, and procedures: pyelonephritis, fluid losses, inadequate ventilation, ureterosigmoidostomy, for example. When one considers the complexity of the changes which may occur in acid-base balance and electrolyte metabolism in the sick surgical patient, the absence of a typical or stable pattern in any one individual is not surprising. In this connection, it has been pointed out by Bradley that at least five serum electrolyte patterns are encountered in uremia.

The respiratory system and the kidneys are among the stabilizers of the hydrogen ion concentration of the internal fluid environment. The occurrence of acidosis and alkalosis in respiratory or renal disease is evidence that either one or the other of these defenses has not compensated for an abnormality caused by the other. Gamble has commented upon the limitations of the respiratory system in achieving a normal *p*H because of faulty control of ventilation or impaired pulmonary function. Singer and associates (8) point out that in metabolic alkalosis a number of factors may interfere with the inhibition of respiration necessary to allow accumulation of carbon dioxide. Our experience indicates that most cases that become problems for the clinician are complex and contain elements of disorders in both metabolic and respiratory spheres (3).

Darrow wrote in 1948 that a wise physician treats patients and physiologic disturbances in patients rather than diseases. He also added, "One cannot outline a simple treatment for electrolyte disturbances, for treatment is based on knowledge of the manifold disturbances of body water and electrolyte that demand various slightly different procedures. One can describe the various possibilities of electrolyte disturbances in man and indicate how these are met." These words apply aptly to the knowledge of acid-base balance today. Justification for the presentation of such chaos has been lucidly presented by Bean who states, "Clinical medicine must concentrate on the particular, watching many things at once, frustrated by variables out of control and many not even known, limited by what it may do in manipulative experiment but alert to make the most of Nature's experiments which no laboratory can duplicate."

SUMMARY AND CONCLUSIONS

1. The method for estimating disturbances of acid-base balance in the blood, described by Singer and Hastings, has been applied seriatim to the study and clinical management of selected surgical patients.

2. Two cases are presented to illustrate the correlation of the clinical features with buffer base-Pa_{CO_2} diagrams and with ionograms constructed after Gamble.

3. Acid-base equilibrium, relatively stable in health, is far from static in sick surgical patients and may be found to shift in a markedly fluid manner when serial observations are made. Variations in individual response to trauma, disease, operation, complications, and treatment create innumerable variables affecting hydrion balance in ways difficult to predict.

4. The important role of ventilation in acid-base balance in surgical patients has been noted, not only by way of the long recognized abnormalities of the lung and chest bellows action, but also through the sensitive, highly responsive chemoreflex control which may be modified by many factors effective during anesthesia, operation, and convalescence.

5. The method has been found clinically useful, not only in the assessment of acid-base balance, but also in clinical management of sick surgical patients, for a broad view of the patient is acquired which compels one to interrelate numerous complex factors and creates thereby improved care of the patient.

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EDITORIALS

PULMONARY EMPHYSEMA

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ALL PATIENTS who are short of breath do not have pulmonary emphysema. Likewise, all patients who have pulmonary emphysema are not short of breath. The pulmonary physiologists have made outstanding contributions to the early recognition of the disease. As a result of their work, pulmonary emphysema can be diagnosed by pulmonary function studies at a stage in the disease when shortness of breath is unrecognized clinically since it can be adequately concealed by the physical fitness of the patient. Medical management may halt progression of the disease in its early stage if the patient can be made to understand the necessity of a rigid regimen of treatment in which he must take an active part for the remainder of his life. There occurs a late stage in the disease, close to the stage of desperation, when it should be recognized that medical management has only relief to offer but no chance of lasting benefit. It is at this period that the patient should be given the benefit of surgical treatment. Surgery can give much relief to the patient in desperate respiratory failure from pulmonary emphysema; however, surgical treatment for these patients results in a rather high mortality.

Pulmonary emphysema may be classified into primary and secondary types. The primary type may be divided further into generalized (diffuse) and localized categories. In the primary generalized type, all areas of both lungs are involved by the disease and all have airway obstruction. Throughout the lungs there is a difference in the degree of pathologic involvement. Some areas of the lungs are less involved than others. The areas of greatest pathologic involvement are useless as physiologically functioning respiratory tissue. For these reasons, there is little difference between the diffuse type with blebs or bullae and the type without blebs or bullae. The difference is seen in the degree of involvement of the lung tissue. In the localized type of pulmonary emphysema, only a local area of the lung is involved by disease. The remainder of the lung is normal and without airway obstruction. Obviously, excision of the diseased area is the treatment of choice for localized pulmonary emphysema. The secondary type of pulmonary emphysema is that superimposed upon a previously existing bilateral generalized lung disease, such as bronchiectasis, tuberculosis, silicosis, sarcoidosis, or other diseases. In these conditions a greater or lesser amount of alveolar membrane and capillary bed is destroyed before emphysema develops. Surgery has nothing of value to offer these patients.

The causation of pulmonary emphysema is not known. The cause of airway obstruction in the beginning of the disease is unknown, but it is thought by many to be related to bronchial irritation, bronchitis, and in some way to a loss of elasticity of the lung. It is generally agreed that forced expiration, even in the early stages of the disease, has a tendency further to obstruct the outflow of air from the lungs. Long continued and often repeated airway obstruc-

tion gradually leads to overdistention of the pulmonary alveoli, a thinning out of alveolar membranes, an obliteration of capillaries, and a breakdown of the alveolar walls with coalescence and finally produces a lung whose volume on full expiration is far greater than that of a normal lung. Once the lung volume on full expiration has become greater than normal, and the elasticity is impaired, there is found in all patients a loss of the normal physiologic principle that holds open the collapsible bronchioles. This normal physiologic principle which holds open the bronchioles is the result of the elastic lung that is held expanded by the closed pleural space in a rigid chest wall. The elasticity of the lung is asserted in a circumferential pull which holds open the bronchioles. Bronchioles normally enlarge in diameter on inspiration and decrease in diameter on expiration. Regardless of the cause for the beginning of pulmonary emphysema, once the disease is fully developed the loss of the normal physiologic principle which holds open the bronchioles becomes the most important factor in continued airway obstruction on expiration. The continued airway obstruction causes progression and perpetuation of the disease. Loss of this principle becomes a perfect check-valve mechanism that causes increased airway obstruction on expiration.

Early in the disease it seems logical that medical management, diligently adhered to and persisted in by the patient, can stop progression of the disease. The patient should avoid any activity, either work or play, that causes dyspnea. It must be recognized that dyspnea causes forced expiration and this in turn increases the airway obstruction. Increased airway obstruction gradually causes progression of the disease. Cough must be controlled since it momentarily is a period of considerable forced expiration. Bronchial irritation or bronchitis can be minimized by the proper use of appropriate drugs and the avoidance of irritating fumes in work or play. Tobacco smoking, especially cigarettes, should be eliminated. The patient should maintain a normal weight.

In generalized well advanced pulmonary emphysema, with or without blebs or bullae, the normal physiologic principle of holding open the bronchioles can be restored to some degree by reducing the lung volume to fit the expiratory volume of the pleural space. When this is considered as a physiologic operation rather than as a procedure to excise the pathologic condition, it makes little difference whether the lung volume is reduced by excising a bleb or bullae or by sacrificing emphysematous functionally useless lung tissue in the lung where there are no blebs or bullae. The results from reduction in lung volume will depend upon the amount of lung tissue that can be brought into use once again by partial relief of airway obstruction. Reduction in lung volume can be carried out by the excision and plication of functionally useless lung tissue. It is usually accomplished by a combination of both methods. Segmental resection or lobectomy should be avoided since these procedures destroy too much of the capillary bed in a lung showing increased pulmonary artery pressure because of an already reduced capillary bed.

In addition to reduction of lung volume, the lung should be denervated by resection of the vagus branches to the lung and by a local sympathectomy consisting of periarterial, peribronchial, and perivenous stripping, resection of the bronchial artery, and resection of the pulmonary ligament. The denervation will relieve any bronchial spasm that may be present. It will change the character of the scanty tenacious bronchial secretion that causes the patient so much difficulty in the morning. There appears to be no other reasonable explanation for the relief of this distressing morning cough following surgical treatment.

The operation should be performed on both sides of the chest. When only one side is operated upon, the benefit gained by surgery is gradually lost by progression of the disease in the lung not operated upon.

Laennec, the first to write about pulmonary emphysema, early in the nineteenth

century, stated ". . . the lungs seem as if confined in their natural cavity and when exposed, instead of collapsing as usual they rise in some degree, and project beyond the borders of the thorax. . . . and it is quite intelligible that if we can diminish the intensity of the cause which keeps up the habitual distention of the cells, we may in the end hope that these will be actually lessened in volume." Laennec identified the disease. The profession must now realize that the disease is showing a gradual increase in incidence because the population is aging. Furthermore, the profession must recognize that pulmonary emphysema can be diagnosed before severe dyspnea occurs. Obviously, it should be realized that medical treatment can control the disease in its early stage. When the disease has progressed to the state where mechanical factors become the important perpetuating cause for further progression of the disease, the patient should be given the benefit that surgery has to offer, since surgical treatment is beneficial in diffuse generalized pulmonary emphysema with or without blebs or bullae.

RENAL ARTERIAL INSUFFICIENCY CAUSING HYPERTENSION

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IN A HUMAN BEING sufficient narrowing of one or both main renal arteries causes functional changes within the kidneys and systemic alterations, the most striking of which are significant diastolic hypertension and considerable nervous tension. Narrowing of a segmental renal artery also gives rise to similar systemic changes, but functional renal disturbances are not readily detected by present techniques.

Although any intrinsic or extrinsic lesion that causes sufficient arterial narrowing may produce this condition, atherosclerotic occlusive disease is the commonest cause, and congenital strictures induced by fibromuscular hyperplasia the second commonest.

The renal mechanism for raising the systemic blood pressure is so sensitive that the renal blood flow to the affected kidney may be preserved at or near normal levels until advanced degrees of stenosis occur. However, in our experience a significant mean pressure differential has regularly been found across the area of stenosis. This differential has been greater than 50 millimeters of mercury in all but 1 of our patients. It is not clear what initiates the renal humoral mechanism, but hormones are apparently elaborated by the renal tissue which eventuate in elevated systemic blood pressure. The gross renal function is preserved unless severe ischemia develops, but even with relatively normal blood flow the tubules of the affected kidney reject abnormal amounts of sodium and water, that is, subnormal amounts appear in the urine. This condition may be detected by quantitative differential renal clearance studies, but these are tedious for the patient and are subject to frequent technical errors. Comparing the qualitative amounts of sodium and water is often misleading because both of these substances are rejected by the tubules. However, if the plasma and urine concentrations of sodium are compared with a substance that is not rejected by the tubules, for example, creatinine, inulin, or urea, a significant relative reduction in the sodium concentration is regularly noted, and this is apparently specific for this condition.

Urinary symptoms are infrequent. Systolic and significant diastolic hypertension have been regularly observed. We have been struck by the extreme nervous tension of these patients, the apparent correlation of this symptom with the development of the pathologic lesion, and its prompt disappearance with anatomic correction of the lesion. Cardiac and retinal changes parallel the degree and duration of the hypertension. The affected kidney may be smaller than its fellow.

The presumptive diagnosis is made by the characteristic renal clearance changes or by arteriographic demonstration of severe stenosis of a main or branch renal artery. The diagnosis is established by demonstration of a significant pressure differential across the area of stenosis as measured at operation. In the absence of a distal patent vessel the diagnosis can be confirmed only by the clinical response to removal of the affected renal tissue. A renogram is not diagnostic but serial studies provide interesting data concerning the effect of reconstructive procedures on the renal blood flow.

For all procedures we prefer the anterior approach, which permits exploration of the renal arteries, kidneys, and adrenals, meas-

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urement of intraluminal pressures in all indicated arteries, and bilateral renal biopsy. Although at present there is some disagreement as to the degree of pressure differential across the area of stenosis necessary to justify the diagnosis of this condition, only routine measurement of these pressures and correlation with the subsequent clinical course will give a final answer. Bilateral renal biopsies give valuable information concerning other renal lesions that may cause hypertension, and they should clarify the confused ideas concerning "protection" the stenosis affords a kidney from the damaging effects of hypertension.

Renal arterial insufficiency may be corrected by removal of the renal tissue distal to the stenosis or by restoration of unobstructed blood flow. Reconstructive procedures are preferable if technically feasible and the patient can tolerate the longer operation. They are mandatory if resection will leave inadequate functioning renal tissue. In elective cases judgment must be exercised not to attempt reconstructive procedures when early or late technical failures are likely.

Nephrectomy may be total or subtotal as indicated. Reconstructive procedures include endarterectomy, resection of the stenosed segment with direct anastomosis, a splenorenal arterial shunt, and insertion of a graft from the aorta. The latter is particularly useful when aortic resection is also indicated. Normothermic interruption of the renal arterial circulation for periods up to 30 minutes is well tolerated, and postoperative oliguria has not been a problem.

Postoperatively, the nervous tension has promptly disappeared. The diastolic hypertension has regularly been reduced, with varying rapidity and degree. Experience has been too limited, to be sure, but apparently the shorter the duration of the hypertension, and the younger the patient, the more prompt is the fall in blood pressure. In most cases of only a few years' duration the pressures have returned to normal or nearly normal levels. There was only 1 late recurrence of hypertension among 15 patients. This was in a man who had had endarterectomy in reduplicated arteries to one kidney, both vessels being quite small. Eighteen months after an initially gratifying response, hypertension has recurred, presumably because of renewed stenosis of one or more of the small vessels.

Since the response to well conceived surgical treatment in carefully selected cases is gratifying, it is important that this relatively uncommon condition be detected, evaluated, and when indicated treated surgically. To aid in clearly defining this condition, to assist in prognosis, and to sharpen the indications for surgical therapy, the surgeon has the responsibility not only to perform indicated therapeutic maneuvers but also to explore the adrenal glands carefully, to explore and measure the arterial pressures in the renal arteries, and to examine both kidneys grossly and microscopically.

THE SURGEON AT WORK

A MULTIPURPOSE GASTROSTOMY TUBE

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TEMPORARY GASTROSTOMY for postoperative decompression recently has undergone a revival. Feeding and suction simultaneously, as described by Pariera and Heeb, was accomplished by threading a small plastic tube through a Foley catheter and then through an anastomosis. However, some investigators found that this procedure interfered with suction.

Since 1957, I have been modifying a No. 20 Foley catheter (5c.c. bag) to serve a multiplicity of purposes. Figure 1a shows the catheter with the balloon trimmed away to provide a feeding channel. The tip beyond the balloon can be tied off with silk, but this is not necessary. The main lumen of the catheter to be used for decompression is opened by cutting 3 or 4 windows into its side at an appropriate level, usually 4 or 5 inches proximal to the tip. Care is taken to avoid cutting into the smaller lumen. Figure 1b shows the catheter in place as an adjunct to vagotomy and Finney pyloroplasty. The fenestrae are seen in a dependent position to drain the stomach. The tip is resting in the third or fourth portion of the duodenum where drip feedings of clear liquids are to be deposited. The exit of the catheter is buttressed with omental fat to prevent leakage upon withdrawal. Note the loose catgut anchoring suture through the posterior anastomotic suture line which prevents the tube from slipping back into the stomach. Since 1957 this tube has been used in 94 patients in conjunction with various abdominal procedures—vagotomy-pyloroplasty, vagotomy-gastrectomy, sphincterotomy, intestinal obstruction, and pancreatitis. To date, there have been no complications referrable to the tube.

Suction by tube is started immediately following operation. On the day after operation, a slow continuous drip of 5 per cent dextrose in water is begun at a rate of 1,000 cubic centimeters every 8 to 12 hours around the clock until the integrity of the operation proximally is assured—3 to 5 days. If more than a few days of drip feeding is required, the solution may be enriched gradually by adding hydrolysed protein and liquid vitamins, as well as a daily requirement of potassium. Milk may be used but this however, tends to plug the small lumen after 2 or 3 days, unless special precautions are taken. For prolonged feeding, the general principles of jejunostomy care can be followed. The entire tube is then clamped and it is left in place as a safety device until the twelfth to fourteenth postoperative day at which time the catgut encircling the sutures will have softened sufficiently to allow it to slip out with ease. The fistulous tract has sealed over promptly in every one of the cases.

This single tube serves the following purposes simultaneously: (1) gastric decompression—avoiding nasopharyngeal irritation and discomfort with attendant pulmonary problems; (2) duodenojejunal feeding—avoiding multiple vein punctures, restriction to bed, and complex parenteral fluid replacement; (3) an avenue for immediate return of bile collected from an associated common duct drainage tube; (4) a simple means of collecting a 12 hour basal fasting specimen of gastric secretion to ascertain the completeness of vagotomy; (5) a prompt means of ascertaining the presence of recurrent or continuing gastric bleeding.

If postoperative bleeding should occur, through and through irrigation can be accomplished with a nasogastric tube. Ice water can be introduced to flush out clots and blood and lower

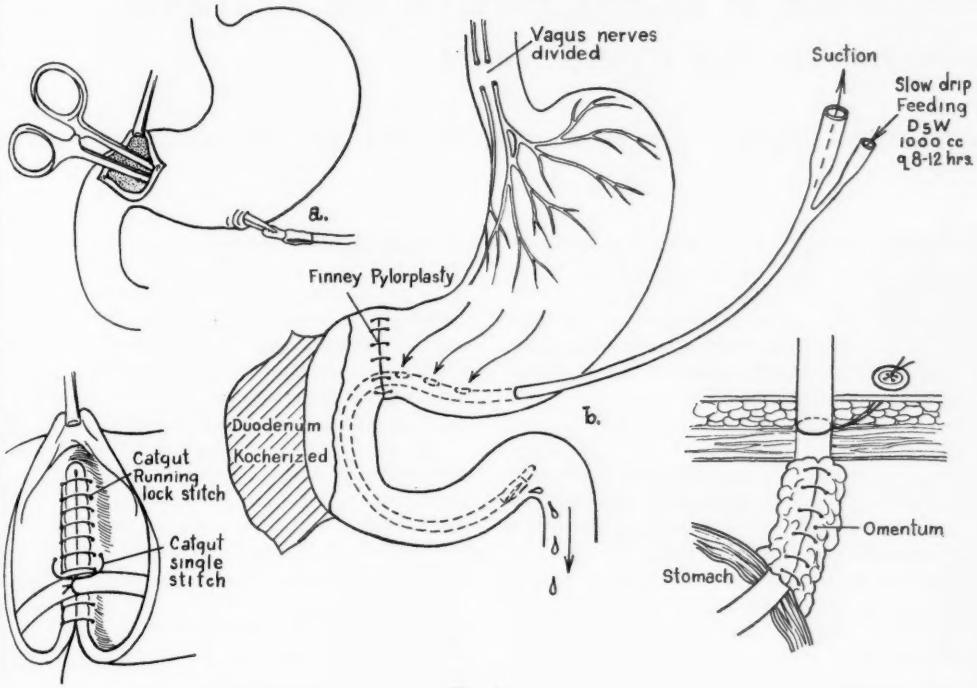

FIG. 1.

intragastric temperature to reduce peptic enzymatic action.

SUMMARY

A multipurpose tube is described which has greatly simplified the care of patients undergoing upper abdominal surgery. Among several other things, it permits simultaneous feeding and suction and makes it possible to avoid nasogastric tubes and intravenous feedings.

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THE SURGICAL SIGNIFICANCE OF THE EXTERNAL LENGTH OF THE CYSTIC DUCT

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CHOLECYSTECTOMY is a very gratifying operation for both the patient and the surgeon, but sometimes it may be followed by troublesome symptoms and signs. In order to evaluate the possible role of the cystic duct in undesirable postoperative sequelae, the external length of the cystic duct was measured.

DATA

All measurements of the cystic duct were made on adults at 40 autopsies in which the gallbladders were normal and at 60 cholecystectomies with or without choledochostomy. In each instance, the cystic duct was isolated from its junction with the neck of the gallbladder to its external junction with the common hepatic duct; the tissue adjacent to the cystic duct was removed by blunt and sharp dissection so that any kinks or convolutions in the cystic duct could be straightened out, and the external length of the cystic duct was determined with a ruler to the nearest 0.2 centimeter (Fig. 1). To avoid stretching of the cystic duct, no tension was placed upon it at the time of measurement.

At autopsies, during which the common bile duct could be opened widely, the termination of the cystic duct was sometimes found to be an intimate part of the wall of the common bile duct for 1 or 2 centimeters. At cholecystectomies no attempt was made to measure this mural portion of the cystic duct, since doing so could result in serious injury to the wall of the common duct. At both autopsies and cholecystectomies, the cystic duct occasionally spiraled around the anterior or posterior aspect of the common bile duct. If this spiral portion was a part of the external length of the cystic duct, it was included in the measurement of the cystic duct.

The values determined in 100 adults are presented in Figures 2 and 3. At 40 autopsies performed on adults who did not have diseased gallbladders, the external length of the shortest cystic duct was 1.2 centimeters; the length of the longest was 5.6 centimeters; and the arithmetical mean was 3.4 centimeters. The lengths of 88 per cent of the cystic ducts varied from 1.8 to 4.6 centimeters, inclusive. At 60 unselected cholecystectomies for cholecystitis with cholelithiasis, the shortest length was 0.6 centimeter; the longest was 5.6 centimeters; and the arithmetical mean was 2.8 centimeters. The lengths of 87 per cent varied from 1.6 to 3.8 centimeters, inclusive.

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DISCUSSION

Previously reported data. In the standard anatomic and operative technique textbooks of Callander, Gray, Shackelford, and Graham and Zollinger and associates, the usual length of the cystic duct is stated to be 2.5 to 4 centimeters.

In 200 dissections on subjects post mortem, Flint found the length of the cystic duct to be from 2.6 to 3.8 centimeters. He noted that, although it is true that the cystic and common hepatic ducts come together at such a point as to give an average of lengths as stated, they do not unite here. He observed that almost always they are merely bound together by fibrous tissue and that by dissection it is possible to separate them from each other for a few millimeters to as much as 2 inches or more.

In a careful study of structures of the cystohepatic angle in 250 cadavers, Moosman and Coller found that the cystic duct varied in length from 0.4 to 6.5 centimeters and that the average length was 3.05 centimeters. They emphasized the importance of prevention of operative injury to the bile ducts in cholecystectomy and supraduodenal choledochostomy.

Comparison of findings at autopsy and at cholecystectomy. For both autopsy and cholecystectomy measurements, the greatest number of ducts were found in the medium length range (Figs. 2 and 3). In general, however, the cystic ducts which were associated with cholecystitis and cholelithiasis, i.e., the cystic ducts measured at cholecys-

tectomy, were shorter than those encountered at autopsies. The inflammation present with recurrent bouts of cholecystitis had undoubtedly led to scarring and contraction of the cystic duct.

The long cystic duct. As indicated in Figure 4, the cystic duct of the diseased gallbladder may be as long as 5.6 centimeters. To visualize accurately and to straighten out the convolutions in the cystic duct, the cystic artery should be ligated and divided, and, if possible, the tissue adjacent to the cystic duct should be carefully teased away from it. Garlock, Glenn, and Hicken and their associates, and Morton have stressed that an incompletely removed cystic duct may lead to postcholecystectomy symptoms by being the site of a small calculus not removed at cholecystectomy or by being the site of postoperative bile stasis and stone formation.

In the following case, inadequate exposure and removal of the cystic duct might have resulted in bile stasis or in calculi forming in the cystic duct remnant. Such calculi could have migrated eventually to the common bile duct.

CASE 1. A 53 year old white female was admitted to the hospital for treatment of recurrent gallbladder complaints of 10 years' duration. She had had a cholecystostomy with removal of calculi from the gallbladder 11 years prior to the present admission. On physical examination, the patient was moderately obese and had upper abdominal tenderness.

At laparotomy, about 1 week after admission, cholecystectomy with removal of several calculi was performed. The cystic duct was unusually long, having an external length of 5.6 centimeters (Fig. 4). The postoperative course was uncomplicated.

The short cystic duct. With repeated bouts of cholecystitis the gallbladder may become scarred and contracted; and, along with such a process, the cystic duct may be shortened and may become intimately adherent to the common bile duct. It is in these cases, in particular, that the cystic duct should be carefully evaluated and that care must be taken to avoid constricting the common duct by operative maneuvers. Putting a suture through the common bile duct wall or placing a clamp on the common bile duct when it is thought to be a part of the cystic duct may result in postoperative stricture. Cole, Coller, Eisendrath, Moosman, and Williams and Williams have emphasized that such accidents may and do happen. Cole has stated:

A large, short cystic duct may give rise to technical complications. Fairly large stones may drop into the common duct, but of more importance is the danger of injury to the common duct while the surgeon is isolating the cystic duct; if the surgeon is not aware of this short cystic duct, he may damage the common duct or excise a piece of it while he is removing the gallbladder.

In the following case, the cystic duct was only 0.6 centimeter long. Inadequate demonstration

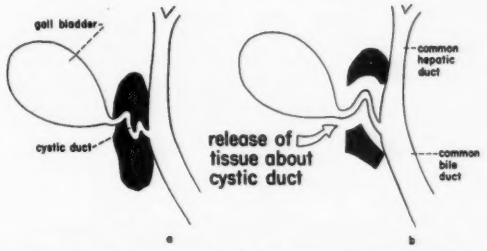

FIG. 1. Measurement of the external length of the cystic duct. The cystic duct is liberated from tissue about it, a, so that the linear length may be measured, b.

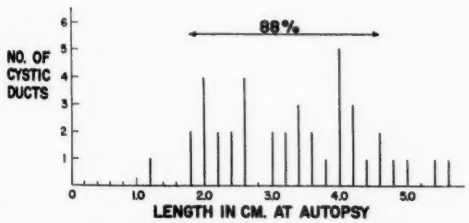

FIG. 2.

FIG. 2. External length of the cystic duct at 40 autopsies in which the gallbladders were normal. Of the ducts, 88 per cent were in the range 1.8 to 4.6 centimeters.

FIG. 3. External length of the cystic duct at 60 cholecystectomies. Of the ducts, 87 per cent were in the range 1.6 to 3.8 centimeters, inclusive.

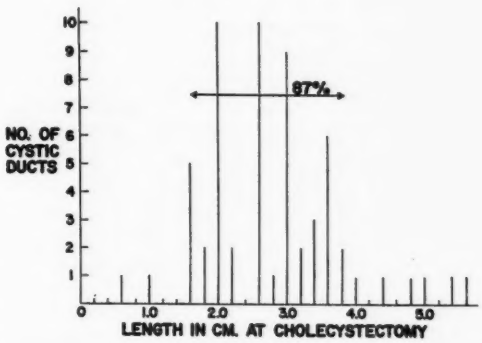

FIG. 3

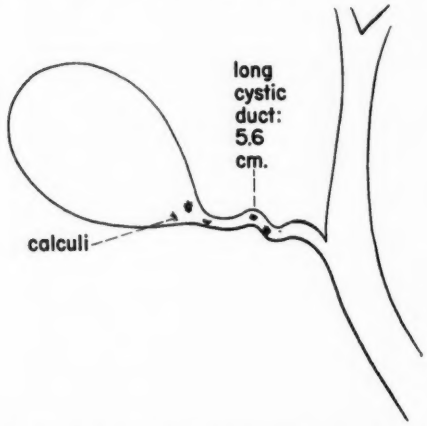

FIG. 4. The long cystic duct (Case 1). Danger is leaving part of cystic duct with calculi.

of the shortness of the cystic duct might have resulted in improper division and ligation of the cystic duct with narrowing of the common duct and possibly postoperative jaundice.

CASE 2. A 61 year old white male was admitted to the hospital for elective cholecystectomy. Previously he had had, for duodenal ulcer, a vagotomy and gastroenterostomy and, for acute cholecystitis, a cholecystostomy.

At operation, cholecystectomy and choledocholithotomy were performed. The gallbladder was contracted to a length of 3 centimeters, and the cystic duct was 0.6 centimeter long (Fig. 5). The postoperative course was uncomplicated.

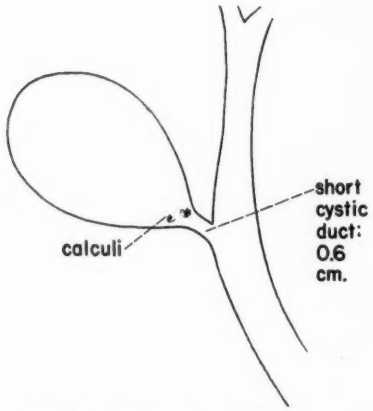

FIG. 5. The short cystic duct (Case 2). Danger is excision of part of common duct or stenosis of duct with suture.

SUMMARY

Measurements of the external length of 100 cystic ducts were made at autopsies unassociated with gallbladder disease and at cholecystectomies for chronic cholecystitis with cholelithiasis.

At autopsy, the external length of the cystic duct varied from 1.2 to 5.6 centimeters, inclusive; and at cholecystectomy from 0.6 to 5.6 centimeters, inclusive.

In view of these differences in the cystic duct, at the time of cholecystectomy the approximate external length of the cystic duct should be noted and the area of the junction of the cystic duct and the common hepatic duct should be recognized before any permanent ligatures are placed about the cystic duct or before the cystic duct is divided. If correctly performed, such operative evaluation of the external length of the cystic duct should result in fewer cystic duct remnants with calculi and fewer common bile duct strictures.

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THE SURGEON'S LIBRARY

The Book Shelf

NEGLECTED GENIUS OF THE NINETEENTH CENTURY

ROBERT S. SPARKMAN, M.D., F.A.C.S., Dallas, Texas

In 1859, J. L. W. Thudichum proposed a two stage cholecystostomy for the management of gallstone colic (6, 7). This was the earliest recommendation for elective operation upon the gallbladder. Prior to this time, operations upon the gallbladder had been confined to those instances in which rupture into or through the abdominal wall had occurred; such operations were limited to enlargement of fistulas or extraction of stones through them.

Little attention was paid to Thudichum's proposal. Eight years were to elapse before Bobbs, unaware of Thudichum's suggestion, performed the first cholecystotomy. In 1878, when Sims performed the first premeditated operation upon the gallbladder, he erroneously credited Handfield Jones with having first suggested such a procedure. Acknowledgment of Thudichum's priority for this proposal first appeared in the discussion of a report by Tait in 1879, 20 years after Thudichum's original suggestion. Thudichum's priority was acknowledged by subsequent writers.

Thudichum, a unique and controversial personality, was far ahead of his time. His work was brilliant, voluminous, and varied. Failure to receive acceptance and recognition of his contributions was a notable characteristic of his fascinating career. Ironically, it was his greatest work, that relating to the chemistry of the brain, which was most vigorously rejected and which induced the enmity of some of the most prominent scientists of his time. Because of this great contribution, later to be verified, he was branded a liar in the scientific press. He never achieved Fellowship in the Royal Society, an honor which he richly deserved. Appreciation of the magnitude and accuracy of his work has come slowly. A splendid definitive biography, complete and rich in detail, is now available. This volume, entitled *Thudichum—Chemist of the Brain*, was published in 1958 by David L. Drabkin of Philadelphia. As a result of this engaging and sympathetic biographic study, Thudichum may achieve the exalted place in medical history which he deserves. All subsequent details concerning Thudichum's life and work have been derived from Drabkin's biography.

Johann Ludwig Wilhelm Thudichum was born 27 August 1829 at Budingen, Germany. His father, George Thudichum, was a Lutheran minister, founder and principal of the Budinger Gymnasium, and a recognized Greek scholar, known for his translations of the tragedies of Sophocles. Thudichum learned the combustion technique of chemical analysis from Liebig at Giessen and studied spectroscopy and spectrophotometry under Bunsen at Heidelberg. From 1850 to 1851 he interrupted his medical career to serve as a voluntary surgeon under Esmarch in the Danish War. In 1853 he emigrated to London. Two years later he became a member of the Royal College of Surgeons. In 1859, after 6 years in England, he became a naturalized citizen. It was in this year, at the age of 30, that he made his proposal for operation upon the gallbladder. Most of his great work was yet to come.

In his lifetime Thudichum published more than 200 scientific articles covering a phenomenal range of subject material. His greatest interest,

however, lay in the relatively unknown field of the chemistry of the brain. To this work he devoted his greatest efforts, continuing his investigations in this field to the end of his life. In an analysis of more than 1,000 human and animal brains, he isolated and identified cephalin, phrenosin, sphingomyelin, galactose, lactic acid, and many other entities. This work earned for him the enduring enmity of his contemporaries who attacked him bitterly in the scientific press. Hoppe-Seyler branded his work as a "patent falsification," while Gamgee wrote that "one might as well supply a formula for bread and butter" as to ascribe a chemical structure to the various substances which Thudichum had isolated from the brain. His masterpiece, *The Chemical Constitution of the Brain*, was first published in 1884, and appeared later in an enlarged and revised edition in 1901, 3 months prior to his death. Years later, in 1930, Thudichum's preparations were to be found in his stable by Otto Rosenheim, noted British biochemist, and were to prove chemically pure. Only then was vindication finally achieved for Thudichum and his work. Drabkin describes Thudichum as the first English biochemist and the world's first pathological chemist.

In the field of gallbladder disease Thudichum made several notable contributions. In 1863, 4 years after his proposed gallbladder operation, Thudichum published a lengthy and classical text, *A Treatise on Gall-Stones: Their Chemistry, Pathology, and Treatment* (8). The first section of this volume contained an exhaustive survey of all previous work bearing on this subject and is a classic in itself. It is noteworthy that this volume contained no reference to the operation which Thudichum had proposed earlier. Moreover, there is nothing to indicate that Thudichum himself ever attempted to perform an operation on the gallbladder. It was he, however, who first propounded the theory of gallstone formation by precipitation or crystallization upon a nidus. He also made fundamental contributions in the chemistry of the bile pigments.

Thudichum became the first Director of the Laboratory of Chemistry and Pathology of St. Thomas' Hospital in 1865, but gave up this position after 6 years, since financial considerations necessitated that he devote more time to private practice. To a large extent, his investigations were supported by the revenue gained from this practice. He became the leading otolaryngologist of his day. He invented the Thudichum nasal speculum which is still in use and devised an electric cautery to be employed in removal of nasal polyps.

Fundamental discoveries of major import were made by Thudichum relative to hemoglobin and urinary pigments; he was also the discoverer of the carotenoid pigments, precursors of vitamin A, which he first isolated from the corpora lutea of the ovaries and later from many additional plant and animal sources. In the field of public health he made notable contributions relative to industrial diseases of miners, sewage disposal, water supply, parasitic infestation of meat, and mange in dogs. He wrote extensively and authoritatively on the chemistry of wine and beer, and even published a large cookbook. He extolled the therapeutic virtues of the Turkish bath and involved himself in considerable controversy on this subject. In 1870 he interrupted his practice to serve as a voluntary surgeon, again under Esmarch, in the Franco-Prussian War; during this time he made repeated demands that nitrous oxide be supplied for operations on the wounded and was ridiculed for these efforts. He was probably the first man to propose that anesthesia be provided for battle casualties. Despite the demands of his practice and his investigations, Thudichum was still able to find time to pursue several hobbies with enthusiasm. He was an excellent musician, a connoisseur of wines, and a grower of prize dahlias.

Thudichum died in 1901. Recognition of his vast accomplishments was to come slowly. In 1930, Otto Rosenheim discovered Thudichum's chemical preparations and notebooks in the stable of the family home in London. The chemicals were contained in bottles numbering in excess of 300, all carefully sealed and labeled in Thudichum's handwriting. The notebooks provided a guide to the specimens. The chemical preparations of the brain first isolated and identified by Thudichum were subjected by Rosenheim to extensive analysis and were found to be chemically pure. The discovery and identification of these specimens established beyond any question the validity and authority of Thudichum's work in this field. The home where Thudichum accomplished so much was destroyed during World War II.

In his book on the chemistry of the brain, Thudichum remarked that "institutes should be set in operation in which not only infectious

diseases but also diseases of the brain and nervous system can be studied with a view toward answering chemical questions as well as the general investigation of the cellular fabric." It is fitting that such an institution now bears Thudichum's name. This commemorative event is described by Drabkin.

"On the outskirts of Galesburg, a small but historic community about two hours by train from Chicago, the State of Illinois has built her own fine hospital for the care and study of the mentally ill, the State Research Hospital. Here, on October 17, 1953, a neglected genius of the nineteenth century, the first chemist of the brain, was memorialized. On this day the new psychiatric research laboratory of the hospital was dedicated as the Thudichum Laboratory and the annual Thudichum lectures were initiated."

The appropriate name was proposed by Dr. Percival Baily of Chicago.

One hundred years have now elapsed since Thudichum proposed elective operation upon the gallbladder. This epochal contribution is now acknowledged on its centennial.

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Reviews of New Books

THERE HAVE BEEN THREE TEXTS on bone tumors reissued in new editions during the past 2 years. The question which immediately arises is, whether or not, yet another such book is worth adding to the library. After examining Coley's volume, *Neoplasms of Bone and Related Conditions*,[1] this question can be emphatically answered in the affirmative. This is a surgeon's book, written by a man who has examined patients, carried out amputations, suffered the frustrations of dealing with bone pathologists, and gained a few victories at great cost in time, effort, and thought. It is devoid of the smugness of some of the pathologic texts in which all diagnoses are very definite and straightforward, with the exception of the case you happen to have at the time. This is a book by a clinician for clinicians and is filled with helpful information on the diagnosis and management of patients with bone tumors and diseases of bone which can be confused with tumors. Emphasis is placed upon the details of management. Two facets of the book deserve special mention. The first is the increased stress placed upon malignant tumors of bone which arise secondarily to, or in association with, preexisting lesions of bone and exposure to radiation. Such secondary tumors are far more frequent than previously supposed, and the recognition of this hazard affords the surgeon an opportunity of preventing some of these tumors by prophylactic excision of their precursors. The second feature is the ample bibliography especially of the classical papers of historical importance. Man's knowledge of bone tumors did not arise solely during the past 25 years, but is as firmly rooted in the past as is any other area of medicine. Many of these articles deserve rereading. This book embodies the results of the long experience of the author in the Bone Tumor Department of the Memorial Hospital for Cancer and Allied Diseases.

—*Leonard F. Peltier.*

THE MONOGRAPH entitled *I tumori retroperitoneali*[2] is an extensive report on the histogenesis, clinical picture, pathologic anatomy, and treatment of the tumors of the retroperitoneal space. The term retroperitoneal tumor as used in this publication is limited to those tumors which stem from the subcutaneous alveolar tissue, blood vessels, lymphatic channels, nerves, and embryonic remnants contained in the posterior and inferior abdominal and pelvic retroperitoneal spaces. Neoplasms of kidneys, adrenals, and pancreas, with well defined characteristics, are not considered.

The presentation of the clinical reports is preceded by a brief exposition of the current views on the embryology and anatomy of the retroperitoneal space, as well as by a short historical note. The clinical material is based upon the authors' personal series of 54 patients observed at the Department of Surgery of the State University Medical School of Milan, Italy. Two chapters are devoted to the histogenesis of the retroperitoneal tumor. This study is made complex by the fact that several embryonic remnants which can undergo neoplastic degeneration at any stage of their development are normally present in the retroperitoneal space, as well as all types of tissues found everywhere else in the body. The subsequent histologic features, therefore, are extremely complex and often difficult to interpret. As a consequence, most of the classifications reported in the literature are unsatisfactory. The authors favor a simplified classification which takes into consideration the histologic origin of the tumor as well as its clinical features.

The clinical picture of these tumors includes pain, presence of a mass, functional impairment of various organs, and general signs and symptoms. Pain is the most common complaint and is present in about one-half of the patients. Pain which is more common in sarcomas and tumors of the nervous system is related to the histologic type of the tumor and to its location. In the absence of pain, the presence of a mass is usually the reason for the patient seeking medical advice. In this series, a mass was present in 38 per cent of the patients. The functional impairment concerned mainly the gastrointestinal tract, 25 per cent, but involvement of the genitourinary system is not uncommon, 9 per cent. The diagnosis of a retroperitoneal tumor is based upon the results of the history, physical examination, laboratory tests, and roentgenologic examination. Roentgenography plays a role of primary importance in this respect, specifically, the aortogram and the retropneumoperitoneum. The aortogram is performed by the usual technique. The contrast medium recommended is 50 per cent hypaque. The retropneumoperitoneum consists of the injection of oxygen into the retroperitoneal space by means of a needle introduced through the anococcygeal ligament. All the details of this interesting technique are given. The prognosis of retroperitoneal tumors is correlated with the histologic type and location of the neoplasm. In the case of histologically malignant tumors the prognosis is extremely poor. In the authors' series of 25 cases of malignant tumors, only 1 patient survived 4 years after surgery. In all cases the treatment consisted of surgical removal of the tumor together with local and regional lymph nodes if involved and when possible, followed by irradiation. Roentgen rays were never employed as a substitute for surgery.

The book is well printed and amply illustrated. The roentgenograms presented are technically perfect and their reproduction is excellent. An ample list of reference is included. —*Ricardo Benvenuto.*

IN THE ERA of relentless medical specialization, Schaffer's *Diseases of the Newborn*[3] although a weighty

[1] NEOPLASMS OF BONE AND RELATED CONDITIONS; ETIOLOGY, PATHOGENESIS, DIAGNOSIS, AND TREATMENT. 2nd ed. By Bradley L. Coley, M.D. 862 pages, 649 illustrations. $30.00. New York: Paul B. Hoeber, Inc., 1960.

[2] I TUMORI RETROPERITONEALI. By G. F. Pellegrini and G. Caraffa, with the collaboration of C. Crosta. 306 pages, illustrated. Turin: Edizioni Minerva Medica, 1960.

[3] DISEASES OF THE NEWBORN. By Alexander J. Schaffer, M.D. 878 pages, 341 illustrations. $20.00. Philadelphia and London: W. B. Saunders Co., 1960.

book of 878 pages is not a narrow discourse. Schaffer is a pediatric practitioner and no section of the book is designed as the ultimate, nor is any topic handled exhaustively in monographic style.

Short chapters, a complete index, double columns, and more than 300 illustrations lend easy readability and attractiveness to this book. There is little doubt that this volume can answer the need of the surgeon who has infrequent contact with infants or the pediatric surgeon who requires a broader knowledge of puzzling medical situations in differential diagnosis.

Two additional features add to the acceptability of this volume: the illustrative case histories and the illustrations. The former are consecutively numbered throughout the chapters and the author has borrowed such histories when necessary from other sources. Forty per cent of the illustrations are from publications of other authors, freeing this work from the fault of many in which illustrative material is chosen because of its exclusive ownership rather than its teaching potential.

One cannot help but wish that common lesions such as inguinal hernia and undescended testicle, apparently so confusing to the pediatrician during the neonatal period, were covered in greater detail and that the neurosurgical chapters emphasized the dangers of diagnostic procrastination. It would also be helpful to the reader to know what might be expected in the way of mortality and morbidity in the treatment of such lesions as congenital malignant tumors and hydrocephalus.

An excellent pharmacopeia for newborns and 3 appendixes on resuscitation in the delivery room, infant care, and management for the erythroblastosis fetalis add concise information in step-by-step outline. More than 100 pages on neonatal cardiology by Milton Markowitz is one of the creditable features of this worthwhile endeavor. —*C. Everett Koop.*

THE MONOGRAPH *Intra-osseous Venography*[4] details the author's experience with roentgenography of regional venous systems by the injection of contrast material into the medullary cavity of certain bony structures. Of particular interest are his methods of visualization of the internal mammary veins, the azygos system, the vertebral venous system, and the pelvic veins.

The volume is curiously uneven. The methods advocated for certain purposes appear to be rather questionable. For example, angiocardiography by injection of contrast material into a costal medullary canal is recommended "should the conventional intravenous approach fail or appear impractical." In fact, occasions when it is impossible to cannulate one of the numerous peripheral veins available for this purpose are so rare as to be almost unknown in the hands of an experienced examiner. In this era of selective angiocardiography, with its numerous advantages, the intraosseous approach for this purpose appears particularly retrogressive. The author states that "... an additional argument in favor of the costal intra-osseous route for angiocardiography is its possibility of opacifying several important intrathoracic veins by one strategically located injection. This particular feature ... may prove attractive ... in order to determine the site and type of compression or displacement of the systemic cardiac inflow tract by mediastinal lesions." No examples of this supposed advantage are included in the chapter on this method. The angiocardiograms reproduced would be considered as unsatisfactory studies by most roentgenologists.

Many of the reproductions in the book are not adequate. One must assume that the original roentgenograms were of sharper quality. Diagrammatic representations of the findings, however, are printed side by side with the reproductions in most cases and are of considerable help in interpreting the findings.

Despite the shortcomings of this monograph, there is a wealth of information available. Although some portions must be approached with a degree of skepticism, the book should be of interest to surgeons, roentgenologists, and anatomists. There are many ideas, a fresh approach to the diagnosis of many conditions, and a method of visualization of certain anatomic areas not easily demonstrated by more conventional means. —*Richard G. Lester.*

THE EIGHTH EDITION of *A Textbook of Surgical Pathology*,[5] first published in 1932, was written by C. F. W. Illingworth, a professor of surgery, and B. M. Dick, a thoracic surgeon. It is very difficult for me to determine for whom this book has been written. It is certainly not for the pathologist for it has been written and repeatedly revised by physicians whose only apparent claim to knowledge of pathology is gross pathology. The illustrations of the gross specimens often stem from the ancient past and have historical rather than practical value. Many are taken from the Museum of the Royal College of Surgeons of Edinburgh. In comparing the 1932 edition with the 1960 publication, it is apparent that a great percentage of the illustrations have not been changed. Those illustrations which are particularly poor include Figures 14, 15, 16, 94, 147, 171, 177, 221, 225, 229, 231, 232, 316, 319, and 321. Figures 15 and 169 are of the same case. The photomicrographs, in a great many instances, are of poor quality, without detail, the small round variety, and, frequently, are out of focus around the periphery (Figs. 9, 23, 26, 74, 82, 114, 116, 130, 158, 197, and 209 are especially poor). The legends for a number of these photomicrographs have no meaning or do not fit in with modern knowledge. The caption for Figure 159 reads: "Malignant thymoma, showing malignant lymphocytic tissue and a concentric laminated body," the meaning of which escapes me. Figure 158 is reputed to be representative of a thymic tumor. The photomicrograph shows nothing recognizable. Figure 23 represents a "mixed-cell sarcoma of bone." I do not understand this term. The legend for Figure 82 reads: "Multiple myeloma. The greater number of the tumour cells are myelo-

[4] INTRA-OSSEOUS VENOGRAPHY. By Robert A. Schobinger, M.D. 245 pages, 317 illustrations. $14.50. New York and London: Grune & Stratton, 1960.

[5] A TEXTBOOK OF SURGICAL PATHOLOGY. By C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S. (Ed.), F.R.F.P.S. (Glas.), Hon. F.A.C.S., Hon. F.R.C.S. (Eng.), and Bruce M. Dick, M.B., F.R.C.S.(Ed.), F.R.F.P.S.(Glas.). 8th ed. 700 pages. 329 illustrations. $10.50. Boston: Little, Brown & Co., 1960.

blasts—primitive white blood cells—in addition to a few giant cells." Multiple myeloma, today, is supposed to be composed of plasma cells. The cells in this photomicrograph cannot be recognized except as little black blobs, and the giant cells seen may be megakaryocytes.

I can say nothing about the references because there are no references. They were eliminated in this edition for the following reason: "To avoid increase in size of the book we have omitted the lists of references formerly attached to each chapter as we believe a student-reader would be unlikely to need them, and because a senior graduate would seek a wider range." Most textbooks quote references which are helpful to the student, whatever age he may be, further to illumine his knowledge or to enable him to read the reference on which a given statement is based. This book contains numerous individuals' names, some familiar and others unfamiliar. These unfamiliar names may be attached to statements which are certainly questionable. In order to find the reference one would have to spend considerable time with the *Index Medicus*.

Now, as to the content—the seventh edition was reviewed in the *Journal of Pathology and Bacteriology*, 1957, 74: 234, and about 25 misstatements were pointed out. Most of these have been checked by me and most of them remain. It is possible to take almost any chapter and to quote many misstatements of fact. For instance, Chapter 35 is on the diseases of the female genital system. All of the information on this problem is given in 32 pages. There is no mention in this chapter about carcinoma in situ. There is a statement that cancer of the cervix is due to the liability of the cervix uteri to laceration or other damage during childbirth. Sarcomas of the uterus are described under headings such as "circumscribed sarcoma" and "diffuse sarcoma." In the discussion of ovarian tumors, there is no discussion of thecoma. The authors state that dysgerminoma is a synonym for arrhenoblastoma. In most instances, there is nothing about the origin of the tumors. This chapter is really worthless.

This book cannot be for the pathologist, and since the gross pathology is inadequate and inaccurate, it cannot be considered a textbook of surgery and it cannot be recommended, therefore, to either surgeon or pathologist. —*Lauren V. Ackerman.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Die Chirurgie des Magensarkoms. By Prof. Dr. A. Gutemann and Dr. H. W. Schreiber. 95 pages, illustrated. $6.80. Stuttgart: George Thieme, 1960.

Early Care of Acute Soft Tissue Injuries. By the Committee on Trauma, American College of Surgeons. 2nd ed. 217 pages, illustrated. $2.25. Philadelphia and London: W. B. Saunders Co., 1960.

An Outline of the Treatment of Fractures. By the Committee on Trauma, American College of Surgeons. 7th ed. 137 pages, 46 illustrations. $1.75. Philadelphia and London: W. B. Saunders Co., 1960.

Wirbelgelenk und Bandscheibe. By Prof. Dr. L. Zukschwerdt, Dr. med. E. Emminger, Dr. F. Biedermann, and Dr. H. Zettel. 2nd rev. enl. ed. 319 pages, 160 illustrations. DM58. Stuttgart: Hippokrates-Verlag, 1960.

Surgical Treatment of Unequal Extremities. By Charles Weer Goff, M.D. 184 pages, 136 illustrations. $11.00. Springfield, Ill.: Charles C Thomas, 1960.

The Normal Skull; a Roentgen Study. By Robert Shapiro, M.D., and Arnold H. Janzen, M.D. 257 pages, 645 illustrations. $18.00. New York: Paul B. Hoeber, Inc., Medical Division of Harper & Bros., 1960.

Pages in the History of Chest Surgery. By Rudolf Nissen, M.D., and Roger H. L. Wilson, M.B., B.Chir. 166 pages, illustrated. $7.50. Springfield, Ill.: Charles C Thomas, 1960.

Nierensymposion, Göttingen 1959; aktiver Ionentransport und Lokalisation des Stofftransports in der niere Bedeutung des Gegenstromsystems füer die Harn-Konzentrierung. Edited by Kurt Kramer and Karl J. Ullrich. 139 pages, 72 illustrations. $6.20. Stuttgart: Georg Thieme, 1960.

Epidemiologic Methods. By Brian MacMahon, M.D., Ph.D., Thomas F. Pugh, M.D., Johannes Ipsen, C.M., Dr. Med. 302 pages, 37 illustrations. $7.50. Boston: Little, Brown & Co., 1960.

The Metabolic Basis of Inherited Disease. Edited by John B. Stanbury, M.D., James B. Wyngaarden, M.D., and Donald S. Fredrickson, M.D. 1477 pages, illustrated. $30.00. New York, Toronto, and London: McGraw-Hill Book Co., Inc., The Blakiston Division, 1960.

Ciba Foundation Colloquia on Endocrinology; Human Pituitary Hormones. Edited by G. E. W. Wolstenholme, O.B.E., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. Vol. XIII, 336 pages, 86 illustrations. $9.50. Boston: Little, Brown & Co., 1960.

Ciba Foundation Symposium on Congenital Malformations. Edited by G. E. W. Wolstenholme, O.B.E., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. 308 pages, 91 illustrations. $9.00. Boston: Little, Brown & Co., 1960.

The Sturge-Weber Syndrome. By G. L. Alexander, M.D., F.R.C.S.E., F.R.C.S., and R. M. Norman, M.D., M.R.C.P. 95 pages, 54 illustrations. Bristol: John Wright & Sons Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

Artefacts and Handling and Processing Faults on X-ray Films. By Prof. Dr. E. A. Zimmer. 67 pages, 128 illustrations. New York and London: Grune & Stratton, Inc., 1960.

Complications in Surgery and Their Management. Edited by Curtis P. Artz, M.D., F.A.C.S., and James D. Hardy, M.D., F.A.C.S. 1075 pages, illustrated. $23.00. Philadelphia and London: W. B. Saunders Co., 1960.

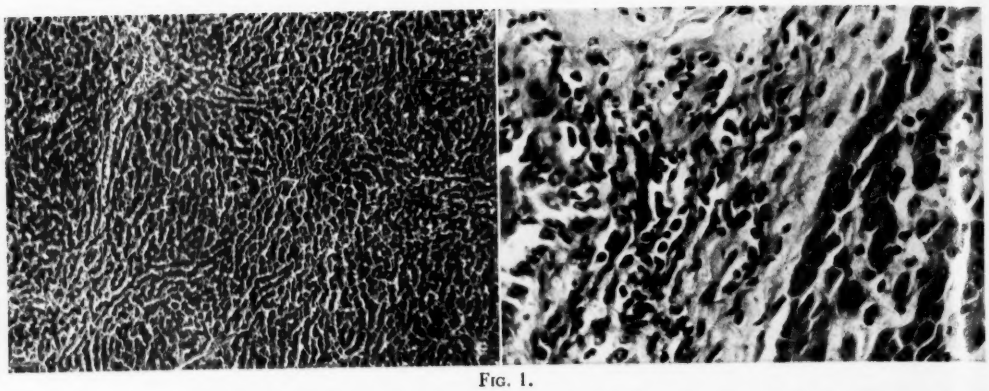

FIG. 1.

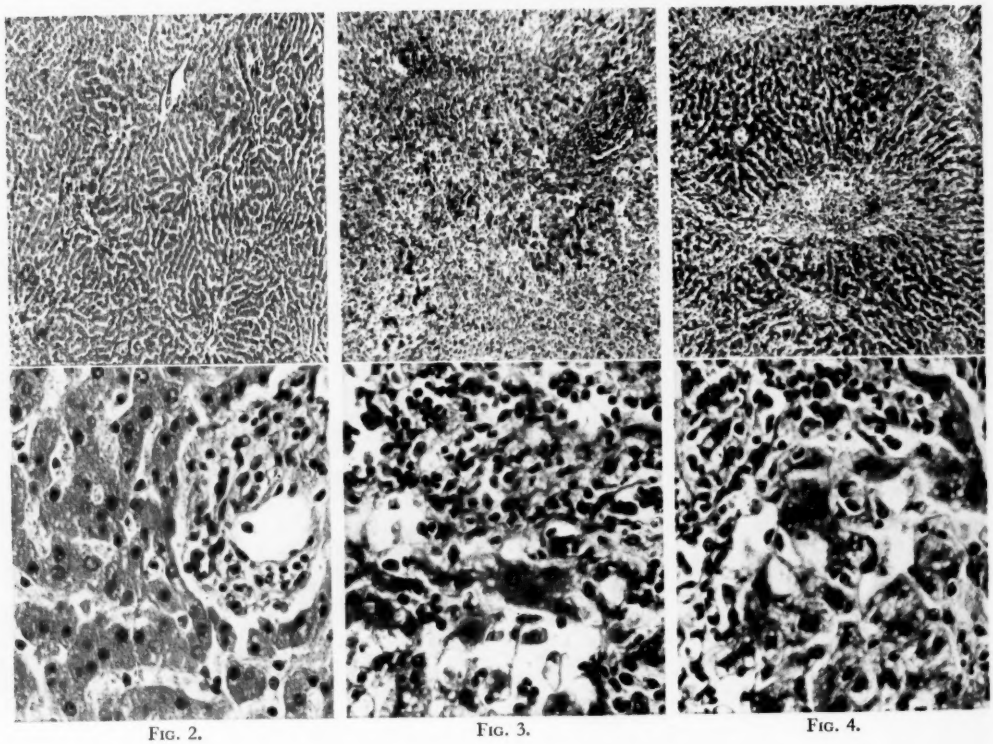

FIG. 2. FIG. 3. FIG. 4.

Appearance of liver homografts at varying times after transplantation.

FIG. 1. Five days: left, ×42; right, ×263.
FIG. 2. Nine days: above, ×42; below, ×263.
FIG. 3. Ten days: above, ×42; below, ×263.
FIG. 4. Twenty and one-half days: above, ×42; below, ×263.

Studies on the Rejection of the Transplanted Homologous Dog Liver.—
Thomas E. Starzl, Harry A. Kaupp, Jr., Donald R. Brock, and James W. Linman.